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ENCEPHALOGRAPHIC STUDIES IN CHILDREN

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ENCEPHALOGRAPHIC studies in children have been made in many clinics, usually with two purposes in mind. First, there have been attempts to determine whether certain clinical syndromes, as for example infantile cerebral palsy, might be correlated with definite encephalographic pictures. From this approach Guttmann[1] studied a series of patients in whom hemiplegia was noticed at birth or appeared during the first year of life, and was able to classify the findings into four groups. Winkler[2] reported the encephalographic findings in a series of seventy-eight patients, all of whom had manifested evidence of mental deficiency in early infancy; in sixteen of these there was a definite history of birth injury. The most common findings in his series were increase in size, asymmetry, and distortion of the ventricles. An interesting collection of films has appeared in publications by Crothers, Vogt, and Eley[3]; Bogin, Holzager, and Kramer[4]; Kruse[5]; Eckstein[6]; and Koschewnikow.[7]

The second purpose in making encephalographic studies in children has been to separate the fixed lesions[3] of the brain from those of a more progressive nature. Actually this is a difficult task; for example a porencephalic cyst, which presumably is a congenital lesion, may be progressive in its course in a manner similar to a brain tumor.

In our own experience, the encephalogram has been of considerable assistance, particularly in separating from the large group of children with convulsions, those children who may be benefited by surgical intervention. Children with convulsive seizures appearing at the onset of an acute infection, or associated with a toxic factor, such as lead, or with a neoplasm, are not included in the study.

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PRESENTATION OF CASES

Eight cases from the records of the Surgical or Pediatric service of the New Haven Hospital have been chosen from a series of about one hundred encephalograms taken over a period of four years. These cases demonstrate a possible uniformity in the encephalographic picture of a specific clinical entity (microcephalic idiocy) and the therapeutic value of air injection in some cases of porencephaly. The main object is to indicate the usefulness of the encephalography in epileptic children with a view to selecting suitable cases for operation, and to suggest the more radical procedure of lobectomy in lesions confined to one lobe.

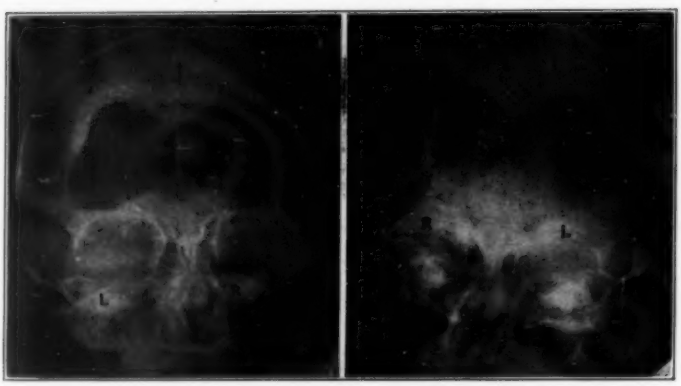

Fig. 1. Fig. 2.

Fig. 1.—(Case 1) Microcephaly with associated porencephaly in a four-and-one-half-year-old boy. Films show advanced symmetrical internal hydrocephalus involving entire ventricular system; no air present in the cortical subarachnoid spaces. Plate taken immediately after air injection. (In all the plates, the arrow indicates the portion of the head which was uppermost while the film was being taken.)

Fig. 2.—(Case 1) Plate taken twenty-four hours after air injection. Air has entered a porencephalic cyst in the left temporoparietal region. The lateral wall of the left lateral ventricle can be seen as a thin gray line.

CASE 1.—J. L., a white boy, four and one-half years old, was admitted to the New Haven Hospital on March 6, 1933, because of convulsions. Birth followed a protracted labor in a primiparous mother, and the resuscitation of the infant was attended by great difficulty. The anterior fontanel was noted to be closed soon after birth. From earliest infancy both mental and physical development had been markedly retarded, with generalized convulsions occurring at frequent intervals. Examination revealed a small, ill-nourished, spastic child showing obvious marked mental deficiency. The cranium was small, measuring 44 cm. occipitofrontal diameter. There were marked contractures of the extremities which were very spastic and occasionally showed athetoid movements. Encephalography (Fig. 1) demonstrated marked enlargement of the lateral ventricles and the third ventricle. The cortical markings were not visualized in any region. A film (Fig. 2) taken twenty-four hours after the air injection showed considerable air in the lateral ventricles with

extension of air from the left ventricle to the parietal bone, similar to that seen in porencephalic defects. The patient was discharged unimproved.

Summary: Microcephalic idiocy in which encephalograms revealed a symmetrical internal hydrocephalus (Fig. 1) and absent cortical markings. A porencephalic defect was visualized in the eighteen-hour films (Fig. 2).

CASE 2.—J. S., a white boy, thirteen years old, was admitted to the New Haven Hospital on December 31, 1931, one hour subsequent to a fall from a slow-moving motor truck. When first seen, the boy was unconscious and was having repeated convulsive seizures during which the extensor tonus of the extremities was increased. The respirations were accelerated; the left pupil was dilated and showed no reaction to light; a diffuse blush extended from the face to the umbilicus and the rigidity of the extremities was greater on the right side. A skull fracture was not revealed by x-ray. A left subtemporal decompression was performed, and, upon opening the dura, approximately 25 c.c. of bloody spinal fluid escaped under considerable pres-

Fig. 3.—(Case 2) Traumatic rupture of the vein of Galen in a thirteen-year-old boy. Film shows a symmetrical enlargement of entire ventricular system. There is noted widening of the sulci on the right and absence of air in the cortical subarachnoid spaces on the left. The cisternae venae magna cerebri are dilated.

sure. With repeated spinal drainage for fourteen days, the fluid gradually cleared and consciousness returned. At this time examination revealed a spastic right hemiplegia with slight weakness of the left side, a dilated left pupil which was fixed to light, bilateral external rectus weakness, and the presence of tonic neck reflexes. The episodes of hyperventilation, increased rigidity of the extremities, and blushing would reappear with slight painful stimulation. These attacks were indicative of extensive brain stem damage and were possibly caused by a traumatic rupture of the vein of Galen. Because of progressively increasing weakness of the left side, encephalography was performed during February, 1932. The films (Fig. 3) revealed a symmetrical internal hydrocephalus, absence of cortical markings on the left and broadened sulci over the right side. There was no evidence of subdural hematoma on the right side. Approximately six hours after the air injection, the patient suddenly became cyanotic, and the respirations became slow and shallow. A lumbar puncture was performed immediately, and complete relief followed the removal of a small amount of spinal fluid. There was some return of function in the left side on discharge from the hospital during April, 1932, although there was definite evi-

dence of psychomotor retardation. When observed ten months subsequent to the injury, the left hemiparesis was quite marked; the mental condition was greatly improved; and petit mal attacks were occurring at infrequent intervals.

Summary: Traumatic rupture of the vein of Galen with clinical evidence of considerable brain stem injury. Encephalograms revealed a symmetrical internal hydrocephalus (Fig. 3). Of interest is the marked respiratory difficulty appearing six hours after the air injection and its subsidence following lumbar puncture.

CASE 3.—W. A., a white boy, fifteen years, old, was admitted to the New Haven Hospital on June 20, 1932, because of convulsions. Birth occurred subsequent to a difficult breech extraction in a primiparous mother at term. "Fainting spells" were described as having occurred on the third day of life, with frequent later recurrences. The mental and physical development had progressed in normal fashion. The first grand mal seizure occurred three months before admission and was followed by similar attacks. There was no aura, or focal nature to the seizures. Examination showed a bilateral primary optic atrophy, a right homonymous hemianopsia, a coarse

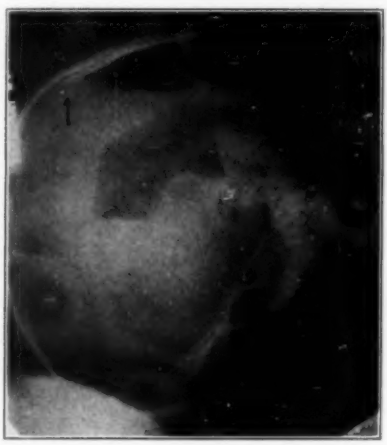

Fig. 4.—(Case 3) Porencephaly subsequent to intracranial birth injury. Film shows porencephalic defect in left occipital region. The left lateral ventricle is not visualized; in the face-down position, the air escaped from the left ventricle into the porencephalic cyst.

cerebellar nystagmus on looking toward the left, and a slight right facial weakness. The encephalograms (Fig. 4) demonstrated absence of the cortical air markings, an internal hydrocephalus and a large porencephalic defect in the occipital region. There was no recurrence of the "fainting spells" or grand mal attacks during his course in the hospital. Because of the unexpected therapeutic result operative intervention was withheld. When seen ten months following the air injection, he was still free from either type of seizure and his general condition was excellent.

Summary: Porencephaly associated with convulsions subsequent to intracranial birth injury in which encephalograms (Fig. 4) demonstrated a porencephalic defect in the left occipital region. No recurrence of symptoms during the ten-month period following air injection.

CASE 4.—H. P., a white girl, sixteen years old, was admitted to the New Haven Hospital on December 10, 1929, because of convulsions. Birth had followed a brief,

spontaneous labor at term, and the early developmental period was normal. A single, generalized convulsive seizure occurred at the age of nine months. She was then free from seizures until the age of nine years when convulsions began to appear at varying intervals. These were preceded by a sensation of numbness, which would originate in the right hand and spread upward along the arm finally to involve the face. This performance was followed shortly by a convulsion, which also originated in the right hand. Loss of consciousness sometimes accompanied the seizures. On examination the patient was found to be mentally retarded. There was a supranuclear right facial weakness and a weakness of the flexor muscles of the right hand. Encephalograms (Fig. 5) demonstrated no enlargement of the ventricles. There was, however, a porencephalic defect in the left occipitoparietal region. A left osteoplastic bone flap was elevated. In the region of the left inferior parietal lobule, the gyri were shrunken and atrophied in an area approximately 4 cm. in diameter. Midway between the angular gyrus and the occipital pole was a porencephalic cyst. Clear spinal fluid was visible through the pia-arachnoid, which formed the lateral wall of the cyst. The lateral wall of the cyst was removed. A prompt

Fig. 5.—(Case 4) Porencephaly associated with microgyria in the left parieto-occipital region. Film shows porencephalic defect in left parieto-occipital region.

cessation of the convulsions followed operation. For three years there was no recurrence of the attacks. On November 25, 1932, the patient was readmitted to the hospital. For several days prior to this admission transient twitchings and a sensation of numbness were noted in the right arm. This was followed by a generalized convulsion on the day before admission. There was now a homonymous right visual field defect in addition to the right facial weakness and weakness of the flexor muscles of the right hand. Her memory and power of concentration were poor. Daily convulsions occurred during the first week in the hospital. Encephalograms were taken, and no new findings were noted. There was a cessation of convulsions eighteen hours after the air injection, and no recurrences were noted during the remainder of her course in the hospital. No convulsions were reported during the six-month period following this admission.

Summary: Porencephaly (Fig. 5) and microgyria in the left parietooccipital region associated with convulsions. Removal of the lateral wall of the porencephalic cyst was followed by disappearance of the seizures for three years. Following a later recurrence of convulsions air was again injected, and no seizures have been reported in the six-month period following the injection.

CASE 5.—J. K., a white girl, four years old, was admitted to the New Haven Hospital on September 28, 1932, because of convulsions. Birth had followed a normal spontaneous delivery at term, and the child's early development had been normal. At the age of three months there occurred a seizure characterized by rigidity, cyanosis and holding of the breath, and similar seizures occurred subsequently. At two years, a generalized convulsion occurred, associated with an elevated temperature, and this performance was repeated six months later. Thereafter, the seizures occurred with greater frequency, and several attacks each day were noted shortly before coming to the hospital. The seizures, at first limited to the right side, gradually became generalized. On examination there was no obvious evidence of mental retardation, and a supranuclear right facial weakness was present. A right hemiparesis appeared subsequent to a convulsive seizure which occurred just prior to operation. Encephalograms demonstrated a moderate symmetrical enlargement of the ventricles. On October 4, 1932, a left osteoplastic bone flap was elevated and a small, pale, softened area was discovered in the mid-parietal region. This was excised. In the Nissl preparation of the excised tissue, there was considerable disturbance of the cyto-architecture of the cortex. There was occasional disappearance of the cortical ganglion cells and proliferation of the glial elements. The nerve cells showed widespread ischemic change, and were shrunken and hyperchromatic. These changes represent a nonspecific degenerative lesion. The convulsive seizures decreased in frequency after operation. However, when seen four months after the operation her general condition was essentially as it had been before coming to the hospital.

Summary: Degenerative lesion of the parietal cortex with convulsions. Encephalograms showed a moderate symmetrical enlargement of the ventricles. Surgical intervention was not followed by relief from symptoms.

CASE 6.—M. D., a white girl, thirteen years old, was admitted to the New Haven Hospital on July 6, 1932, because of convulsions. Birth was at term in a primiparous mother and was aided by instruments. The neonatal course was uneventful and development was normal. The initial convulsion occurred in the fifth year. Subsequently, the seizures became more frequent, generalized, and were associated with unconsciousness. During the month prior to admission, the convulsions had assumed a Jacksonian character and were confined chiefly to the right side of the face and arm. When examined, the child was in status epilepticus. The attacks, clonic in nature and confined to the right side of the face and arm, were repeated in close succession. There was a complete right hemiparesis, more marked in the upper extremity. Encephalograms (Fig. 6) were taken and disclosed the temporal horn of the left lateral ventricle to be definitely larger than the right. In view of the focal nature of the seizures, a left osteoplastic bone flap was elevated. The cortex appeared normal. The face and arm areas, identified by monopolar galvanic stimulation, were excised. Stimulation of these areas before excision had produced a typical convulsion. Microscopically, the excised tissue demonstrated swelling of the ganglion cells with proliferation of the glial elements. The nuclei of the ganglion cells were swollen, vesicular, and an absence of the Nissl apparatus was noted in the cytoplasm. Other ganglion cells were shrunken, hyperchromatic, and showed corkscrew-like axones. These changes are similar to those found in acute and chronic degenerative lesions of the cerebral cortex, and are not characteristic of a specific etiology.

When seen nine months after operation her condition was essentially unchanged from that originally noted.

Summary: Jacksonian epilepsy associated with a degenerative process in left motor area. Encephalograms (Fig. 6) showed a dilated temporal horn on the left. No relief followed surgical intervention in this case.

CASE 7.—A. Z., a white girl, twelve years old, was admitted to the New Haven Hospital on December 4, 1931, because of convulsions. The patient was born at term following a normal spontaneous labor. Her development was uninterruptedly

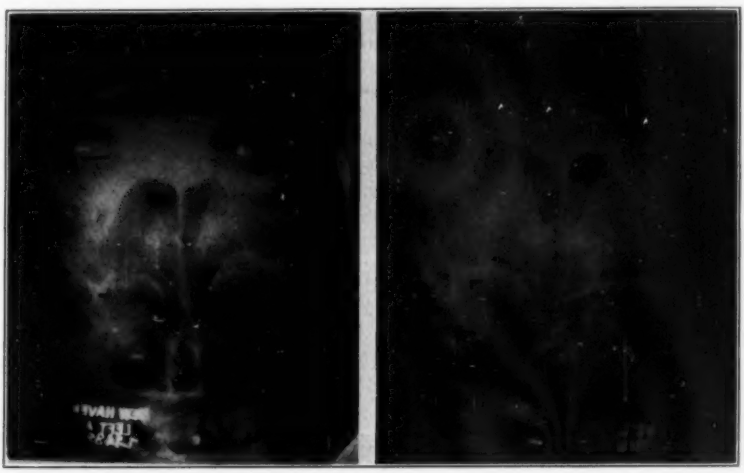

Fig. 6.—(Case 6) Jacksonian epilepsy associated with a degenerative process in the left motor area. Films taken in the lateral recumbent position, showing the left lateral ventricle to be larger than the right, especially in the region of the temporal horn. In this figure and subsequent ones, the margins of the ventricles have been outlined with dots.

Fig. 7.—(Case 7) Encephalomalacia in right temporal lobe due to thrombosis. Film shows the right lateral ventricle to be larger than the left; the ventricular system is shifted slightly to the right.

normal. At six years, a severe convulsion occurred five days after a difficult tooth extraction. Subsequent attacks were noted at irregular but frequent intervals. Shortly before admission, seizures were occurring three times daily. The patient volunteered the information that on several occasions preceding an attack she had

seen "a man with dogs" appearing in her left visual field. Examination revealed a supranuclear left facial weakness, and sluggish abdominal reflexes on the left side. Encephalography (Fig. 7) was performed and showed the right lateral ventricle to be larger than the left and a slight shift of the ventricular system to the right side. The cortical markings were more distinct on the left side. At operation the entire right temporal lobe was found to be pale and soft. An old thrombosis of a cortical branch of the middle cerebral artery was found. A small piece of the cortex from the superior temporal convolution was removed for biopsy. On microscopic examination, the excised tissue showed edema and pallor of some ganglion cells, while others were shrunken and hyperchromatic. The child was discharged from the hospital unimproved. When last seen fifteen months following operation, her condition showed little change over that originally noted in the hospital.

Summary: Encephalomalacia in right temporal lobe due to thrombosis of a branch of middle cerebral artery. Encephalograms (Fig. 7) revealed enlargement

Fig. 8. Fig. 9.

Fig. 8.—(Case 8) Microgyria confined to the left temporal lobe. Film shows enlargement and displacement of left lateral ventricle in case of microgyria confined to left temporal lobe, erroneously interpreted as cortical scar. Third ventricle present in midline. Plates are not entirely satisfactory because the ventricles were not completely emptied of spinal fluid.

Fig. 9.—(Case 8) Microgyria confined to the left temporal lobe. Plate taken in lateral recumbent position. The left temporal horn appears to be ectopic in position because of dilatation. No ventricular shift present as exists in instances of cortical scar. Third ventricle shadow seen in midline.

of the right lateral ventricle with a shift of the ventricular system to the right. A bone flap was elevated and the right temporal lobe was found to be soft and pale. Considering the encouraging result in Case 8, a lobectomy would seem advisable at a later date.

CASE 8.—H. P., a negro girl, six years old, was admitted to the New Haven Hospital on June 13, 1932, because of convulsions. Birth was at term and followed a normal spontaneous labor. At two years, the mental level was below normal, and at this time the first convulsion appeared. The seizures usually began on the right side but became generalized during each episode. The attacks originally occurred

at monthly intervals and later at weekly intervals. The child was left-handed, and there was left-handedness in the family. Examination revealed a spastic, right hemiparesis with a right hemiatrophy, and a supranuclear right facial weakness. The mental age was approximately forty months. Encephalograms (Figs. 8 and 9) showed marked dilatation of the left ventricle, principally in the region of the temporal horn. These findings were interpreted as indicative of a left cortical scar. An osteoplastic bone flap was elevated in the left temporoparietal region, and the dura was found to be normal. The temporal gyri were small, pale, and the entire lobe was of a soft consistency. Minimal galvanic stimulation was attempted, but a convulsion was not produced. The temporal lobe was excised; the specimen removed measuring 4.5 cm. from the anterior pole to the line of section. The convalescence was quite satisfactory, and there were no convulsions reported in the six-month period after operation. Microscopic examination of the tissue removed showed a wide band of acellular tissue replacing the fourth cortical lamina. The nerve cells in the other layers lacked a definite Nissl apparatus. Many nerve cells were shrunken and hyperchromatic and had indistinct nuclei and corkscrew-like processes. The type of cell injury resembled the "sclerotic" type of cell damage of Nissl.

Summary.—Microgyria confined to the left temporal lobe. Encephalograms (Fig. 8) showed a markedly dilated left lateral ventricle, principally in the region of the temporal horn. Clinical findings interpreted as indicative of a cortical scar although at operation microgyria were found in the left temporal lobe. Lobectomy was done and in the six-month period since operation, no convulsions have been reported.

TECHNIC

Avertin anesthesia has proved quite satisfactory in keeping the patient quiet during the procedure. The spinal needle is introduced with the child lying on its side, in order to estimate first the spinal fluid pressure. The child is then placed in the sitting position, and a three-way stopcock, which is designed to accommodate a spinal manometer and a syringe, is attached to the needle so that the procedure may be carried out without disconnecting any part of the apparatus. An attempt is made to draw off all the spinal fluid available, in order to avoid the confusion which may arise from shadows cast by undrained fluid.

The child is maintained in the sitting posture until the anterior, posterior, and lateral views of the ventricles are taken. The remainder of the examination is completed with the patient reclining. An excellent visualization of the temporal horns can be obtained by directing the rays posteroanteriorly with the child in the lateral recumbent position. By placing the patient on his back in an extreme opisthotonic position so that the top of the head is parallel with the floor, lateral and anteroposterior views of the third ventricle can be obtained. A small stool may be placed under the shoulders to obtain the arched posture. Then by turning the patient over on the stool and with the top of the head still parallel to the floor, lateral views of the fourth ventricle can be taken.

An anterolateral view is taken eighteen hours after the air injection for two reasons. First, the ventricular filling is often found to be more adequate in the second examination; and second, defects may appear in the later films which failed to appear in the earlier plates. After becoming accustomed to the normal distention of the ventricles, which appears in the eighteen-hour plates, this phenomenon does not cause confusion.

COMPLICATIONS

Mild meningeal reactions occur quite frequently following the lumbar injection of air. Eley and Vogt[8] reported that the pleocytosis in the spinal fluid was usually mild (up to 300 cells), but counts of 2,000 to 3,000 were occasionally encountered. Several proposals for minimizing the meningeal reaction have been advanced. Liberson[9] has found that filtration of the gas through water prior to injection obviates the post-injection pleocytosis; and that the substitution of inert gases such as helium lessens the severity of the headache. Along similar lines, the cisternal injection of air has its adherents, because less air is required for an adequate filling of the ventricles. However, the obvious risk in such a procedure counterbalances its advantages.

There is little available data in regard to the late complications of these meningeal reactions. Jacobi[10] repeated the air injection in four cases of schizophrenia at intervals of four months and two years after the first injection. In the original films, the cortical air markings were normal; in the subsequent films, however, these markings were absent. The author was of the opinion that these changes resulted from a pia-arachnoiditis, but he was unable to decide whether this leptomeningeal reaction was associated with the mental disease or secondary to the air injection. In the reports of pathologic studies in cases of schizophrenia, no reference has been made to pia-arachnoiditis.

In a series of about one hundred consecutive lumbar injections (adults and children), complications of a serious nature were encountered in only one instance. (Case 2.) The history of another child with strikingly similar evidence of a brain stem lesion (decerebrate posture and tonic neck reflexes) has come to our attention. The child was three months old, and the history was essentially one of extremely difficult labor followed by convulsions and generalized spasticity. A lumbar air injection was made at another hospital, and the child died several days later. It is quite probable that in the presence of a brain stem lesion, the injection of air, with its subsequent increase in intracranial pressure, is sufficient to embarrass the vital centers to the extent of producing respiratory paralysis.

DISCUSSION

Microcephalic idiocy is merely a clinical grouping, and even as such is ill defined; as the name implies, extreme smallness of the cranium is its distinguishing feature, and in a well-marked case the small cranium contrasts strikingly with the relatively large face below it. According to Still,[11] "more than half the cases of imbecility, including all varieties, have the head below the normal size, but very few of these would be classified as microcephalic." Case 1 presented clinically the closest possible approximation to the criteria for the diagnosis of microcephalic idiocy. In four cases of microcephalic idiocy, we have found symmetrically enlarged ventricles and absent cortical air markings, and we consider these findings suggestive of cerebral maldevelopment. The encephalographic evidence alone, however, cannot be dogmatically accepted as diagnostic criteria in the differential diagnosis between cerebral maldevelopment and cerebral birth trauma. It has been pointed out that the usual results of birth trauma are an internal and external hydrocephalus and distortion of the ventricles.

Kruse reported the history of a microcephalic idiot, in whom a large porencephalic defect was visualized in the twenty-four-hour film; a defect which had apparently not filled with air immediately after the air injection. A similar occurrence was noted in Case 1 of our series. These findings throw some light on the explanation of the cessation of seizures (Cases 3 and 4) after the air injection. A porencephalic cyst may be intermittently obstructed from its communication with the subarachnoid space or ventricle; and such a temporary obstruction might produce a convulsion by transient changes in intracerebral pressure relations. The delay in the filling of these porencephalic defects with air would seem to support the assumption that a block has been formed due to adhesions, which are broken up by the air.

Certain radiographic pictures will eventually come to be associated with certain definite cerebral lesions as has been accomplished with cortical scars[12] for example. To attain this end, a lumbar injection of air should be made in a child with convulsions prior to surgical intervention, even though there be no question as to the localization of the lesion. In this manner, certain cases may be excluded as unsatisfactory for surgery. When the encephalogram shows no definite abnormalities or only a symmetrical enlargement of the ventricles, surgery is not indicated despite the fact that the seizures or neurological signs are of a localizing nature. A symmetrical enlargement of the ventricles is indicative of a diffuse process, in contrast to a rather circumscribed enlargement of one temporal horn, for example,

in which case the lesion is more likely to be of a focal nature. We have had this experience in three cases and have presented Case 5 as an example. Lobectomy is indicated in lesions rather sharply confined to one lobe as in Case 8, which was an instance of microgyria confined to the left temporal lobe. If the improvement in this case continues, it would seem advisable to perform a lobectomy in Case 7 also. The assumption is that the threshold of excitability is lowered in the area involved by the pathological process. It has been shown experimentally by Amantea,[13] Clementi,[14] and Spiegel[15] that it is possible to produce epileptiform attacks after localized strychninization on the cortical center of a sensory organ by exciting the respective peripheral organ. Spiegel concludes that "in these cases the excitability of the respective sensory centers is increased by the strychnine to such a degree that the impulses entering here from the periphery will not remain localized to the respective sensory center, but irradiate to the remaining cortex, first of all to the motor region thus causing an epileptiform attack."

CONCLUSIONS

1. The encephalographic findings in eight selected cases are discussed in this communication.

2. Serious complications have not been encountered except in a patient with a brain stem lesion.

3. A rather uniform encephalographic picture has been found in four cases of microcephalic idiocy. One of these cases is reported.

4. In two instances of porencephaly, convulsive seizures stopped after the air injection.

5. By taking twenty-four-hour films, defects may be visualized which failed to appear in the plates taken immediately after the air injection.

6. Encephalography has been found to be of assistance in choosing from a group of epileptic patients those children who may be benefited by surgical intervention; the indications for operation are discussed.

7. Lobectomy was done for a patient with microgyria confined to the temporal lobe with encouraging results.

We wish to acknowledge our appreciation to Dr. William J. German, who performed the operative procedures, and to Dr. Harry M. Zimmerman, for his assistance in studying the pathologic material.

REFERENCES

1. Guttmann, L.: Med. Klin. 26: 886, 1930.
2. Winkler, H.: Arch. f. Psychiat. 91: 495, 1930.
3. Crothers, B., Vogt, E., and Eley, R.: Am. J. Dis. Child. 40: 227, 1930.
4. Bogin, M., Holzager, T., and Kramer, B.: Am. J. Dis. Child. 42: 526, 1931.

5. Kruse, F.: Ergebn. d. inn. Med. u. Kinderh. 37: 332, 1930.
6. Eckstein, A.: Ibid. 32: 531, 1927.
7. Koschewnikow, A. M.: Fortschr. a. d. Geb. d. Röntgenstrahlen 36: 1180, 1927.
8. Eley, R. C., and Vogt, E. C.: Am. J. Roentgenol. 27: 686, 1932.
9. Liberson, F.: Am. J. M. Sc. 185: 478, 1933.
10. Jacobi, W.: Deutsche Ztschr. f. Nervenh. 112: 266, 1930.
11. Still, G. F.: Common Disorders and Diseases of Childhood, Oxford Med. Pub., 3rd ed., London, 1920, p. 588.
12. Foerster, O., and Penfield, W.: Brain 53: 99, 1930.
13. Amantea, A.: Boll. Soc. Ital. Biol. Sper. 1: 387, 1926.
14. Clementi, A.: Ibid. 3: 4, 1928.
15. Spiegel, E. A.: J. Nerv. & Ment. Dis. 75: 504, 1932.

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THE CAUSE OF DEATH IN INFANTILE ECZEMA

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THE possibility of a rapidly fatal termination in a disease so relatively benign as infantile eczema has given rise to many theories regarding the nature of these deaths.

The mysterious blanching of the skin, which sometimes occurs prior to death, brought about the lay tradition that it is dangerous to "drive in" the eruption. The significance of this incident remains as obscure today as it was when first commented on three centuries ago. The identification of these accidents with status thymicolymphaticus classifies but fails to explain many of the deaths. Whatever connection there is between eczema deaths and status lymphaticus, the classification should certainly be reserved for those instances in which the relationship is established by a meticulous clinical and pathological technic. Thymus hyperplasia, with its attending diathetic state, is far from being proved as the cause of many of the sudden deaths attributed to it.

In 1902, Feer,[1] in a paper read before the Gesellschaft für Kinderheilkunde discussed the sudden deaths of eczematous infants. He regarded the thymus gland as the responsible factor. V. Ranke, discussing his paper, reported sixteen rapid deaths in a period of ten years. Five of these were without thymus hyperplasia. Judassohn in a large dermatologic practice had not seen sudden death occur but had witnessed relatively frequent bronchopneumonia.

The dermatologist's lack of familiarity with this particular phase of eczema end-results is perhaps explained by the fact that these results are not usually seen in private practice. Conversations with various dermatologists lead us to believe that these unfavorable end-results with eczema are equally unheard of in the occasional eczemas treated in hospitals for adults. They have been particularly noted in those infants hospitalized in children's hospitals, the earliest medical contribution on these accidents having been reported by Wyss from the Zurich Children's Hospital in 1895.

Hutinel[2] was the first to call attention to the factor of septicemia as a cause of sudden deaths of these infants. He regarded the hos-

The author wishes to express his appreciation to Dr. S. M. Markson of the Department of Dermatology, Milwaukee Children's Hospital, for assistance in the critical analysis of the case histories.

pital milieu as an unfavorable background for these infants with a diminished defense mechanism. Similar observations were published by Hulat, Sauvain, Barthelemy and others.

In a recent communication, the writer called attention to the high institutional mortality of infantile eczema.[3] This report records the clinical findings and necropsy reports in infants hospitalized for the treatment of eczema who died as a result of a rapidly developing toxemia. These infants were admitted for the treatment of eczema alone; the report does not deal with cases in which there were other reasons for hospitalization.

These ten instances are taken from the records of the Milwaukee Children's Hospital. Their treatment was directed by the respective dermatologists on service at the hospital. No one plan of treatment was used. The various details of therapy are not recorded, since it is very evident from a perusal of these methods that no relationship exists between the unfavorable result and the procedures used.

CASE REPORTS

CASE 1.—J. H., born June 4, 1925; aged three months, eleven days; hospital stay forty-six days.

Admitted to the hospital Sept. 15, 1925, with fairly severe eczema of seborrheic character, involving face, scalp, neck, and arm flexures. Temperature normal; weight normal for age. Sept. 16, slight temperature rise noted; Sept. 21, temperature 102°, otitis media, weight gain; Oct. 11, eczema improving; Oct. 26, eczema quite improved, temperature 100°; Oct. 27, onset of severe toxic symptoms, temperature 105°; watery stools; Oct. 28, very toxic, dehydrated, temperature 104°; Nov. 1, expired.

Diagnosis: Intestinal intoxication. No postmortem examination.

Summary: Onset of toxic symptoms with watery stools forty-two days after admission; death four days later.

CASE 2.—D. F., born November 29, 1926, was admitted to the hospital March 22, 1927, aged three months, twenty-one days; hospital stay thirteen days. Mar. 22, fairly severe extensive eczema of head, face, trunk and extremities; temperature 98.2°; well nourished. Mar. 30, upper respiratory infection; temperature 103°; sudden onset of toxic symptoms; eczematous skin improved; Apr. 4, definite signs of bronchopneumonia; expired suddenly.

Summary: Toxic symptoms, pyrexia, upper respiratory infection eight days after admission with septic symptoms and bronchopneumonia.

CASE 3.—E. H., born June 9, 1926, was admitted February 25, 1927, aged eight months, sixteen days; hospital stay thirty days. Feb. 25, infected, crusted eczema seborrheicum in subacute relapse; scalp-facial type; temperature 101.2° on admission; bronchitis noted; Feb. 28, eczema improving; evidence of pneumonia, toxic symptoms; Mar. 2, sudden death.

Postmortem: Lungs showed a few congested patches.

Blood Culture: Pure pneumococcus.

Diagnosis: Infantile eczema complicated by pneumococcus septicemia.

CASE 4.—C. L., born August 4, 1925, was admitted February 25, 1926, aged six months; hospital stay seven weeks. Feb. 25, well nourished; temperature 98.2°; eczema of scalp-facial type, severe subacute relapse, oozing edematous, crusted, extension to trunk and extremities, infection; Mar. 3, skin somewhat improved; Mar. 15, skin improved but weight loss 10 ounces in seventeen days (on restricted low fat diet); Mar. 23, temperature 103°; sudden onset of toxic symptoms; localized findings: (1) otitis media acute; (2) infected conjunctivitis, keratitis; (3) upper respiratory infection; (4) bronchopneumonia; April 12, temperature 103°; severe toxemia; skin shows subacute eczematous relapse; weight loss 1 pound, 8 ounces; the same day sudden, unexpected collapse; expired.

Summary: Baby six months old in good general health admitted with severe eczema; twenty-eight days later sudden onset of pyrexia, otitis media, acute septic symptoms, upper respiratory infection; death from sepsis and bronchopneumonia twenty days later.

CASE 5.—L. M., born December 8, 1927, was admitted March 22, 1928, aged three months, fourteen days; hospital stay fourteen days. Mar. 22, well-nourished infant, eczema scalp-facial type, acute edematous relapse, fairly severe, temperature 98.4°; Mar. 30, very abrupt clearing of skin, loss of weight in one week (1 pound, 1 ounce); Apr. 2, temperature 101°, slightly toxic, no clinical signs; Apr. 5, sudden overwhelming toxemia, temperature 101°, collapse and sudden death.

Postmortem Examination: Thymus weighed 5 grams. Anatomic diagnosis: Bronchopneumonia. Blood culture: No growth.

Summary: Normal three-month-old infant with severe eczema admitted with normal temperature; lost weight rapidly in spite of nonrestricted lactic acid milk feedings; very rapid clearing of skin, three days later pyrexia and toxemia; sudden collapse and death. Although the blood culture was negative, the course was one of overwhelming septicemia.

Clinical Diagnosis: Septicemia.

CASE 6.—P. M., born November 6, 1927, was admitted March 17, 1928, aged four months, eleven days; hospital stay six days. Mar. 17, normal child, temperature 98.3°, beefy, weeping infected eczema of scalp-facial type; Mar. 18, temperature 102°; Mar. 20, temperature 103°; skin clearing, seven ounces weight loss in three days; Mar. 21, temperature 102.5°; skin clearing, toxemia noticeable; Mar. 23, temperature 103.5°, skin clear, child toxic, listless, apathetic, loss of weight one pound, six ounces in five days; death.

Postmortem Examination: Anatomic findings—bronchopneumonia; thymus 12.5 grams; blood culture—streptococcus; diagnosis—streptococcus septicemia.

Summary: Normal infant, normal temperature, eczema of severe localized face-scalp type in subacute relapse—(1) pyrexia developed twenty-four hours after admission; (2) progressive clearing of the skin; (3) progressive loss in weight; (4) fulminating type of sepsis on the fifth day; (5) sudden death on sixth day after admission; (6) clinical diagnosis: septicemia.

CASE 7.—E. S., born July 10, 1929, was admitted September 9, 1929, aged two months. Sept. 9, impetiginous eczema of face, trunk, extremities, with severe subacute relapse, temperature 100°; acute otitis media; Sept. 12, discharged and sent home because of deaths of previous cases, skin somewhat improved; Sept. 23, readmitted, eczema aggravated, right ear draining, temperature 103°; toxemia; Sept. 28, temperature 105°, very septic, bronchopneumonia noted; Oct. 3, severe sepsis, bronchopneumonia, expired.

CASE 8.—D. W., born September 21, 1929, admitted September 30, 1930, aged one year; hospital stay five months. Sept. 30, rachitic child; history during early

infancy showed facial eczema, which gradually subsided; present admission because of severe, subacute, generalized eczematous relapse of two weeks' duration. During the months of October, November, December, 1930, and January, 1931, there was little change. The skin condition improved and relapsed several times during this period. Feb. 3, 1931, upper respiratory infection, temperature 102°; mild toxemia, purulent rhinitis; Feb. 8, otitis media, severely septic, very ill, dehydrated; Feb. 12, expired.

Clinical Impression: Pneumonia.

Postmortem Examination: Anatomic findings: bronchopneumonia, thymus, 10 grams (normal); pericardial fluid culture: Streptococcus and pneumococcus.

Summary: Older child, about a year old, and beyond the nursling period, was in the hospital several months before complications developed.

CASE 9.—R. M., born December 27, 1928, admitted June 10, 1929, aged five and one-half months; hospital stay thirty-six days. June 10, severe, subacute, eczematous relapse of scalp-facial type of eczema, infected, also involving the extremities; June 13, 17, 20, condition not much improved by local medication; June 24, slight pyrexia, temperature 101° fourteen days after admission, no clinical signs accounting for pyrexia, no septic symptoms; June 29, improvement of the skin condition, drop in fever; July 2, sudden rise of fever to 104°; clinical finding—injected throat, acutely relapsed eczema; July 4, general, and skin improvement; July 5, bronchitis and gastrointestinal upset, toxic symptoms, gradual decline in weight, gradually increasing severity of toxic symptoms; July 16, death, two weeks after the onset of toxemia and eleven days from the onset of the gastrointestinal symptoms.

Postmortem Examination: Cause of death—intestinal intoxication; anatomic diagnosis—gastritis, enteritis, and colitis.

CASE 10.—A. K., born May 20, 1928, was admitted November 27, 1928, aged five months, seven days; hospital stay eighteen days. Nov. 27, face, scalp, body subacutely relapsed eczema rubrum, temperature 98.2°; Dec. 1, four days after admission, upper respiratory infection, temperature 103°; Dec. 5, eight days after admission, fifteen ounces weight loss, temperature 102°; not severely toxic; diet—whole milk mixture; Dec. 11, toxic, acute bronchitis, acute otitis media, temperature 103°, leucocytosis; Dec. 15, severely toxic, sudden death.

Postmortem Examination: Thymus and lungs, normal; blood culture—*Streptococcus hemolyticus.*

Summary: Five-month-old infant admitted November 27 in otherwise good health, for care of severe eczema; three days later upper respiratory infection, pyrexia; eight days later acute bronchitis, otitis media, severe loss in weight; ten days later sudden toxic death.

Clinical Diagnosis: Septicemia.

SUMMARY

Of ten infants who died following admission for the treatment of infantile eczema: four showed septicemia; four others had a fulminating type of bronchopneumonia; and two died with intestinal intoxication. Whatever the complication causing death, the infants were uniformly very toxic during the last illness. This toxemia was usually associated with rapid weight loss and dehydration. In a few, a sudden collapse was almost the only clinical evidence preceding the disastrous result.

Of the four infants with septicemia, streptococci were found in the blood stream in two, streptococci and pneumococci in one, and a pure culture of pneumococcus in one.

Necropsy was performed in six of the ten cases. The anatomical diagnosis in three of these was bronchopneumonia; in one, bronchopneumonia with septicemia; in one, septicemia alone; in one, enteritis and colitis. In none was there an enlarged thymus gland.

The experience of a rapidly overwhelming infection in the life history of the hospitalized infant is not a new one to pediatrists.[4] The infant with eczema seems particularly vulnerable to such infections. In the group of infants here reported, these infections occurred at variable periods following hospitalization. The severity of the eczema did not seem to be a deciding factor in the occurrence of complications. The kind of food was not a factor, but sudden weight loss was often an early sign of impending disaster. While some infants showed a coincident clearing of the skin during the onset of the severe infection, others did not. Some of these infants were in open wards; others developed their infections despite the fact that they were in cubicles or single rooms, the customary children's hospital technic prevailing.

CONCLUSIONS

What then is the cause of the deaths of these infants admitted for the treatment of eczema? Whatever the peculiar biologic phenomena that make the immunologic responses of the eczematous infant different from that of the normal infant, the deaths here reported impress one as varying, in degree only, from the respiratory deaths seen in hospitalized infants. One feels with Hutinel that, "Ces Septicémies hospitalières ne sont, du reste, pas l'apanage des affections de la peau; elles peuvent se voir du cours de toutes les maladies." (These hospital septicemias are not, however, the accompaniment only of affections of the skin; they may be seen in the course of all maladies.)

I propose no new explanation for the greater violence of reaction seen in these eczematous infants. Another purpose moves me to record these unhappy end-results. It is to direct attention again to the dangers of hospitalizing certain types of infantile diseases. This danger is quite well appreciated in its academic aspects. Resident physicians of children's hospitals are particularly familiar with the catastrophic complications of minor illnesses in the infants' ward. Experienced pediatrists have long witnessed the unsatisfactory results of the institutional treatment of infants, warned of its dangers, and suggested measures for its control.[4, 5, 6, 7]

Even while we recognize the objections to hospitalization as valid, we are soon distracted from the conscious realization of the danger. We witness striking cures, achieved by technic and procedures available only in a hospital. We see children with mastoiditis, empyema, appendicitis, and even stranger maladies, admitted and discharged cured. The idea soon becomes established in our minds that the sick child, the sick infant, the infant needing any sort of care, belongs in the hospital. The administrative side of the hospital, not as acutely aware of these events as the clinicians and naturally bent on having beds filled, helps maintain the illusion of a limitless beneficence. On our service in the infants' ward we are too apt to have an impersonal interest in cases, and institutional casualties do not shock us as much in infants as they do in older children. We end by accepting these incidents as part of our hospital experience.

The relatively small number of infantile eczemas seen at any one time in a children's hospital blurs our sense of responsibility. We fail to realize the frequency of the catastrophic result in infantile eczemas. Seeing them as problems in dermatology and pediatrics soon disperses any misgivings that we might have for an introspective moment, regarding the human side of the question.

Every now and then the instruction to hospitalize is reaffirmed.[8] The infant with eczema has to be restrained "and for this and other reasons, the treatment of severe infantile eczema is a hospital problem." A questioning note has been recently sounded by Hill.[9] In the last few years he has changed his viewpoint regarding the need of hospitalization. "The trouble with hospitalization is that eczematous infants are very prone to infection, especially respiratory infection, and an eczematous infant put into a ward with other infants is very likely to develop otitis media, bronchitis or bronchopneumonia, *no matter what precautions are used.*" (Italics are mine.)

Sepsis, pneumonia and intestinal intoxication, the causes of death in the eczematous infants of this series, are all but variants of upper respiratory tract infection—the common danger of all hospitalized infants. This danger, more than the particular diagnosis in the given eczema death, should be on our minds and consciences. Whatever technical advantages the hospitalization of the eczematous infant may provide, a resourceful medical therapy should find means of affording these advantages outside of an infants' ward. The Speedwell plan[10] "so humanely conceived by Dr. Chapin" offers a rational solution. In properly supervised boarding homes, we may obviate the dangers of cross infection of the hospital and at the same time secure the objectivity often difficult to achieve in the infant's own home.

REFERENCES

1. Feer, E.: Cor.-Bl. f. Schweiz. Aerzte **34**: 45, 1904.
2. Hutinel, V., et Rivet, L.: Arch. de Méd. d. enf. **12**: 1, 1909.
3. Schwartz, A. B., and Koch, D.: J. PEDIAT. **2**: 169, 1933.
4. Brennemann, Joseph: Am. J. Dis. Child. **43**: 577, 1932.
5. Jacobi, A.: Collectanea **8**: 11, 1909.
6. Abt, Isaac: Proc. Children's Hospital Assoc. Indianapolis, 1925, p. 29.
7. Meyer, L. F.: Über den Hospitalismus der Säugling, Berlin, 1913, S. Karger.
8. Becker, S. W.: J. A. M. A. **97**: 983, 1931.
9. Hill, L. W.: J. PEDIAT. **2**: 133, 1933.
10. Chapin, H. D.: Tr. Sec. Dis. of Child., A. M. A., Philadelphia, 1931, p. 173, also J. A. M. A. **98**: 40, 1932.

2018 EAST NORTH AVENUE

A NEW PERTUSSIS ANTIGEN

Preliminary Clinical Report

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THE isolation by Bordet and Gengou[1] of a suspected causal agent from whooping cough patients was followed by many attempts at vaccine therapy. A survey of the literature dealing with results of such treatment leads to no definite conclusion regarding the therapeutic efficacy of pertussis vaccines, and in general, the trend of opinion in the United States at least has been on the negative side, so that the vaccine has been discontinued from new and nonofficial remedies.

Considerable doubt has even been expressed concerning the rôle of the Bordet-Gengou bacillus in whooping cough. However, its constant association with the disease,[2] the occurrence of specific complement fixing antibodies in the blood of convalescents[3, 4] and the favorable results claimed particularly by Madsen[2] and by Sauer[5] in specific vaccine treatment and prophylaxis of pertussis implicate the organism beyond reasonable doubt and offer encouragement for further work along these lines.

METHOD OF ANTIGEN PREPARATION

Krueger, Nichols and Frawley[6] have recently described a method for the preparation of a new pertussis antigen. This method of antigen preparation from endotoxin-producing cells such as streptococcus, gonococcus and *Bacillus coli* had previously been developed by Krueger.[7] The essential feature of the process is the physical disruption of the living cells with the extraction of the endocellular elements without the use of heat or chemicals, in order to obviate denaturation reactions.

Recently isolated strains of *Hemophilus pertussis* grown on human blood-enriched media are utilized. Human blood is employed for two reasons: first, because it is most suitable for maintaining the highly

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antigenic "phase I" of Leslie and Gardner[8] and second, because the use of foreign serums involves the possibility of serum adsorption on the surface of bacterial cells to an extent sufficient to cause sensitization to the serum proteins.

The cells are harvested in buffered isotonic solution, thoroughly washed to remove metabolites, and then mechanically disrupted in a special type of ball mill.[9] The resultant suspension is subjected to ultra-filtration through acetic collodion membranes[10] of such porosity that all intact cells are retained while material in solution or in a finely dispersed phase passes through without substantial reduction in concentration such as occurs when Chamberland or Berkefeld candles are employed.

The water-clear filtrate contains then, those constituents of the live cell put into solution or suspension by physical rupture of the cell membrane. We attempt to exclude two classes of substances both of which we consider to be immunologically undesirable; namely, cell metabolites and denaturation or degradation products resulting from the heat or chemical treatment of the bacteria.

TECHNIC OF ANTIGEN INJECTION

The antigen, as supplied for clinical trial, represented at first the extract from seven billion organisms per milliliter. Later the concentration was increased to twelve billion organisms per milliliter. Before the antigen was used in the treatment of actual pertussis, skin tests were carried out on a group of 300 school chidren, the majority of whom had not had pertussis. One-tenth c.c. was injected intracutaneously and observations made during the next two days. There was usually no local reaction to be seen. In some there was an erythematous patch the size of a dime, which appeared in a few hours and disappeared in twenty-four hours. As a further check, a few normal children were given subcutaneous injections of 1.0 c.c. or 2.0 c.c. with negligible local reactions.

Ample clinical material for testing the prophylactic and therapeutic value of the antigen was furnished by an epidemic of pertussis which has been present in Northern California from December, 1932, to May, 1933. The disease was moderately severe. Treatment was carried out in the home and in a special clinic. In almost all cases, cough plates were obtained. They were about 83 per cent positive.

When the antigen was first used in treatment, 0.1 c.c. was given intracutaneously and 0.1 c.c. subcutaneously. Injections were given daily, gradually increasing the subcutaneous dose until 1.0 c.c. was being given. In some cases, especially in clinic patients, injections were given every other day, increasing 0.25 c.c. each time until the dose reached 1.0 c.c. The parents were usually anxious for daily dos-

age since they claimed that the child rested better after receiving the injection. No arbitrary rules have been laid down with regard to dosage although it seems that better results are obtained with larger doses.

CLASSIFICATION OF RESULTS

In classifying the results of therapy in this series of cases, we have endeavored to bear in mind the danger of attributing to antigen therapy a favorable result since many light and atypical cases of pertussis occur normally. On one occasion a positive cough plate was obtained from an unvaccinated child who had a mild cough for only a day or two with no whooping or vomiting.

In order to evaluate our results, it was necessary to adopt certain arbitrary standards. All cases were classified into two broad groups: first, those in which injections were begun after exposure but before the onset of symptoms; and second, those who were already coughing when first seen. In order to classify the response to treatment in each of these groups, we have used the terms "Good," "Fair," and "Poor."

A case was classified as yielding a "Good" response when there was a marked favorable change in the course of the disease. Severe symptoms, such as whooping and vomiting, lasted in this group not more than one week. A "Fair" response was obtained when severe symptoms lasted from ten days to two weeks, after beginning treatment. A "Poor" response was obtained when no noticeable change took place in the expected duration of the disease. It is hard, however, to escape the conviction that even these cases were beneficially influenced. Generally the appetite was good, and there was little loss of weight. Complications were strikingly absent; there was no mortality.

TABLE I

35 cases. Treatment instituted after exposure but before the onset of symptoms. No symptoms, 14 cases. Those who developed symptoms, 21 cases.		
Good	Fair	Poor
16 (76%)	3 (14%)	2 (10%)

Table I shows the results obtained in a group of thirty-five children treated before the onset of symptoms. Most of them were members of families with clinical cases. Fourteen children developed no symptoms whatever and may be ruled out on the possibility that they were not sufficiently exposed or were naturally immune. Of the remaining twenty-one who developed the disease, sixteen (76 per cent) went through a very mild attack, usually without whooping or vomiting.

Three (14 per cent) ran a moderate course, and two (10 per cent) had severe whooping cough apparently uninfluenced by the vaccine.

TABLE II

165 cases. Treatment instituted after the onset of symptoms.	Group I 86 cases Seen within one week.	Group II 79 cases Seen later than one week after onset.
Good	59 (69%)	36 (45%)
Fair	16 (19%)	33 (43%)
Poor	11 (12%)	10 (12%)

Table II shows the results obtained in a group of 165 children treated after the onset of symptoms. Of eighty-six seen early, fifty-nine (69 per cent) gave a good response; sixteen (19 per cent) gave a

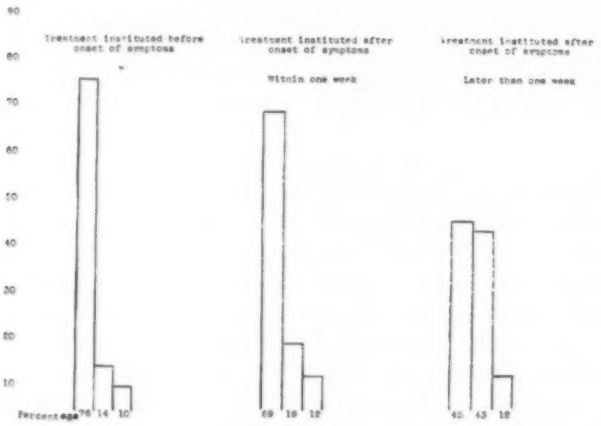

Chart 1.

fair response; while eleven (12 per cent) gave a poor response. Of seventy-nine cases seen later, thirty-six (45 per cent) gave a good response; thirty-three (43 per cent), a fair response; and ten (12 per cent), a poor response.

Chart 1 is a graphic representation which shows definitely that the best results were obtained in those cases treated in the earlier stages.

SUMMARY

1. The material for our study represents a cross-section of a pertussis epidemic waging in California in the winter and spring months of 1932-1933. It was the general consensus of opinion among observers that this epidemic was the severest in six years, as to incidence, and that it was moderately severe so far as the virulence and duration of the disease was concerned.

2. Injection of a new pertussis antigen was given to 200 children after exposure or during the course of whooping cough. Fifty-five cases were treated in Fresno by one of us (J. M. F.) and the other 145 were treated at the University of California Hospital (by M. S. and A. P. K.).

Thirty-five children received injections after exposure but before any symptoms had appeared. Fourteen developed no symptoms. Of the twenty-one of those who went on to clinical pertussis, 76 per cent had a favorable therapeutic response.

One hundred and sixty-five children were first seen during the actual course of the infection. Eighty-six of these had been coughing less than one week. Sixty-nine per cent of this group gave good response to treatment, with cessation of severe symptoms in less than a week. Seventy-nine were seen later than one week after the onset of coughing. Treatment in these was not particularly successful, only 45 per cent showing a cessation of severe symptoms within a week.

3. There was very little local and no constitutional reaction. The absence of such reactions would preclude the possibility of any significant incidence of nonspecific response.

4. Our series gives evidence of the protective value of the antigen although this protection is not absolute. Those patients treated prophylactically who later developed the disease ran a definitely modified course.

REFERENCES

1. Bordet and Gengou: Ann. Inst. Pasteur. 20: 731, 1906.
2. Madsen, Thorvald: Boston M. & S. J. 192: 50, 1924.
3. Chievitz and Meyer: Ann. Inst. Pasteur. 30: 503, 1916.
4. Sauer and Hambrecht: J. A. M. A. 95: 263, 1930.
5. Sauer, Louis: J. A. M. A. 100: 239, 1933.
6. Krueger, A. P., Nichols, V. C., and Frawley, J. M.: Proc. Soc. Exper. Biol. and Med. 30: 1097, 1933.
7. Krueger, A. P.: J. Infect. Dis. 53: 237, 1933.
8. Leslie and Gardner: J. Hyg. 31: 423, 1931.
9. Krueger, A. P.: J. Infect. Dis. 53: 185, 1933.
10. Krueger, A. P., and Ritter, R. C.: J. Gen. Physiol. 13: 409, 1930.

T. W. PATTERSON BUILDING

THE IMMUNIZATION OF SCHOOL CHILDREN AGAINST WHOOPING COUGH

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THE value of vaccine therapy in a disease so variable in duration and severity as whooping cough is difficult to gauge. The difficulty has been due chiefly to two causes: firstly, proper distinction has not been made between the use of the vaccine as a prophylactic and a curative agent; and secondly, as Gardner and Leslie[1] have pointed out, most of the vaccines in general use have been entirely lacking in the specific antigenic principle. These two confusing factors have been kept in mind in the present report which deals with the prophylactic effect of a specially prepared pertussis vaccine in which an effort has been made to preserve the specific antigenic properties.

The vaccine used was the undenatured antigen of H. Pertussis described by Krueger, Nichols, and Frawley.[2] This antigen was prepared from smooth pathogenic types of the organism which were grown on human-blood-enriched media and the endocellular elements extracted by mechanical disruption and ultrafiltration. The filtrate which constituted the antigen solution was diluted to contain in each cubic centimeter the extract from seven to nine billion organisms.

The use of human blood in the culture medium obviates the danger of foreign serum adsorption. As a result, there is very little local and no general reaction from the use of this antigen. Following the injection of 1 c.c. of the vaccine, there is usually an erythematous area about 2 cm., rarely 5 cm., in diameter which appears in six or eight hours and disappears in twenty-four hours.

A preliminary report of the use of this antigen in the treatment of whooping cough was made by Frawley, Stallings, and Nichols.[3]

For prophylactic study the pupils in the kindergarten, first, second, and third grades in five public schools of Fresno, California, were selected. Three hundred and forty-five of those who had not previously been exposed to whooping cough were given a series of injections of the antigen.

Controls: Adequate controls were provided by those classmates, who had not had whooping cough, but whose parents did not wish them to receive inoculations. Pre-school children, in the same families as school children who developed whooping cough, were also taken as controls. The control group was comprised of 614 children.

Dosage: Injections were given weekly or every other week. The latter interval had to be adopted because of the difficulty of furnishing adequate supplies of antigen with experimental laboratory equipment. The first injection consisted of 0.1 c.c. intracutaneously and 0.1 c.c. subcutaneously; the second injection of 0.1 c.c. intracutaneously and 0.5 c.c. subcutaneously; and the third and fourth injections of 1.0 c.c. each given subcutaneously.

Results: Vaccination was carried out during the months of January and February, 1933. Shortly after vaccination was completed, an epidemic of whooping cough began to spread through the schools. From the time that the first case appeared until the end of the school term, June 6, the daily attendance lists were checked and follow-up visits were made to the home of each child who was reported absent. Cough plates were taken in every instance where there was any coughing. Repeated home visits were made and detailed daily histories were kept in each case until the child returned to school. At the end of the school term, the epidemic was still in progress but follow-up work was then impracticable.

A study of the histories of the individual cases in the vaccinated and control groups brings out the following points:

1. The vaccinated children had definitely milder infections than the unvaccinated. One noticeable feature was that they rested well at night with practically no coughing severe enough to disturb sleep. There was little whooping or vomiting. In fact, in many cases it was only by means of a cough plate that a diagnosis of whooping cough could be made.

In Table I comparison is made between the vaccinated and unvaccinated cases with regard to the severity of the infection.

TABLE I

	VACCINATED NUMBER OF CASES	UNVACCINATED NUMBER OF CASES
Mild	26 (62%)	7 (12%)
Moderate	10 (24%)	26 (43%)
Severe	6 (14%)	27 (45%)
	42	60

2. During the three months from the date of vaccination until the closing of school forty-two of the vaccinated children (12 per cent) and sixty of the unvaccinated (10 per cent) had contracted whooping cough. Thus there was apparently no difference in incidence between the two groups. It is possible that this may have been partly due to the short time which elapsed between vaccination and exposure and also to the fact that the dosage of vaccine was small.

DISCUSSION

The prevention of a disease as serious in its effects and complications[4] as whooping cough is deserving of more attention than it receives at present. During the course of this study it was frequently found that positive plates were obtained on children in both the vaccinated and unvaccinated groups, children who were attending school and who were evidently in the catarrhal stage of whooping cough. Nevertheless, they were allowed to remain at school because they were not whooping.

Besides adequate methods of quarantine, more consideration must be given in the future to the question of prophylactic vaccination.

Pierret[5] has observed that, if proper quarantine measures were carried out and prophylactic vaccination were resorted to, at least whenever there was danger of an epidemic, whooping cough could be turned from one of the most serious into one of the least important diseases of childhood. He voices the enthusiastic opinion held by French physicians, that with a properly prepared vaccine in which the antigenic principle has not been destroyed by heat, definite protection can be given. He advises yearly inoculations to maintain immunity throughout childhood.

Sauer[6] has used a special type of pertussis vaccine sterilized without the use of heat. A fairly severe local and general reaction follows the large dose which he gives as a prophylactic measure. However, he has employed it in a large series of cases with success and claims that in at least eight instances children have been thoroughly exposed after vaccination without acquiring whooping cough.

The most convincing evidence of the value of prophylactic vaccination is furnished by Madsen's classic report[7] of the Faroe Islands epidemic of 1923. In a recent paper,[8] he has given the figures for the 1929 epidemic when prophylactic vaccination was even more successful.

SUMMARY

1. Four weekly injections of an active pertussis antigen were given to 345 school children at the onset of a whooping cough epidemic in Fresno, California.

2. Controls consisted of 614 children in the same age group, who had not had whooping cough and who were not vaccinated.

3. During the three months which followed, forty-two (12 per cent) of the vaccinated group and sixty (10 per cent) of the unvaccinated group developed whooping cough.

4. There was a marked difference between the two groups in the severity of the infection. In the vaccinated group, 62 per cent of the

cases were mild, 24 per cent moderate, and 14 per cent severe. In the unvaccinated group, 12 per cent were mild, 43 per cent moderate, and 45 per cent severe.

5. Further study is being made with increased dosage and concentration of the antigen.

REFERENCES

1. Gardner, A. D., and Leslie, P. H.: Lancet 1: 9, 1932.
2. Krueger, A. P., Nichols, V. C., and Frawley, J. M.: Proc. Soc. Exper. Biol. & Med. 30: 1097, 1933.
3. Frawley, J. M., Stallings, M., and Nichols, V. C.: J. PEDIAT. 4: 179, 1934.
4. Frawley, J. M.: Am. J. Dis. Child. 46: 346, 1933.
5. Pierret, R.: Proc. Roy. Soc. Med. 25: 1329, 1932.
6. Sauer, L. W.: J. PEDIAT. 2: 740, 1933.
7. Madsen, T.: Boston M. & S. J. 192: 50, 1925.
8. Madsen, T.: J. A. M. A. 101: 187, 1933.

T. W. PATTERSON BUILDING

PERTUSSIS

Determination of Immunity by Means of Cutaneous Test

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ANY method which would aid in the diagnosis of whooping cough or in the determination of the presence or absence of immunity to the disease would be of great value to the clinician. Modigliani and deVilla[1] found that the intracutaneous injection of Bordet-Gengou bacilli gave a positive reaction in pertussis, but not in other diseases, and that normal children gave negative reactions. Garzia[2] obtained somewhat similar results in a small group of children. Orgel[3] in a preliminary report also stated his belief that there was possible value in the method since he found that those suffering from pertussis usually had a positive reaction, whereas those suffering from other diseases did not. Riesenfeld[4] and Hull and Nauss,[5] however, found that the skin test gave conflicting results and did not believe that it was of diagnostic value or that it indicated the presence or absence of immunity.

In view of the conflicting reports, it appears to be worth while to record our own results in skin-testing with the Bordet-Gengou bacillus. We have employed vaccine prepared after a method similar to that of Sauer.[6] This consists in fresh organisms suspended in a physiologic solution of sodium chloride to which 0.5 per cent phenol is added. One to two minims were injected intracutaneously into the forearm. Readings were made at frequent intervals, seventy-two hours being the preferable time for determining the reaction. An area of redness of over 1 cm. in any diameter was considered positive. This was usually accompanied by local induration. Control tests were performed which determined that the phenol was not responsible for the reaction. A number of tests made with ordinary commercial pertussis vaccines caused little or no reaction and were comparable in no way to the test material which was routinely employed.

Table I indicates the readings obtained on 186 persons.

It is seen that 80.0 per cent of persons tested who had not had pertussis according to the history gave a positive reaction, whereas 76.4 per cent who had had the disease did not react. The history of the occurrence of pertussis is sometimes doubtful, but in the series of patients studied we felt that the data were quite reliable.

From the Wilhelm and Gette Beckman Dispensary of the United Jewish Social Agencies, Cincinnati, Ohio.

TABLE I

PERTUSSIS	NEGATIVE HISTORY	POSITIVE HISTORY
Positive reaction	90	13
Negative reaction	18	55
Suspicious reaction	5	5

Tables II and III show a division of the persons studied into age grouping.

TABLE II

UNDER TEN YEARS

PERTUSSIS	NEGATIVE HISTORY	POSITIVE HISTORY
Positive reaction	81	6
Negative reaction	16	36
Suspicious reaction	4	5

TABLE III

OVER TEN YEARS (INCLUDING ADULTS)

PERTUSSIS	NEGATIVE HISTORY	POSITIVE HISTORY
Positive reaction	9	7
Negative reaction	2	19
Suspicious reaction	1	

In the course of the study several significant incidents occurred. Almost invariably when there was more than one child in the family who had a negative test with a negative history, the readings for all were consistently negative. In two such families, four children had been directly exposed to pertussis at frequent intervals for several months, yet none of the children contracted the disease.

Additional work is now being carried out in which children who have contracted pertussis are being skin-tested at intervals during convalescence. In the few cases so far tested, we have found that in almost all of them the skin test became negative during the fifth week after the onset.

Also a group of twenty-five children who had been skin-positive and who had received the immunization treatment were tested after a period of four months. Twenty of this group became skin-negative, while five remained skin-positive. Four months later the skin-test was repeated on four of the five positive patients, and all were negative.

SUMMARY

It would appear from this study of the skin reactions of 186 persons that there is considerable merit in determining the presence or absence of immunity to pertussis by the intracutaneous injection of

fresh Bordet-Gengou bacilli. A negative test usually indicates immunity, and a positive one susceptibility. The test has been found of assistance in determining in exposed children whether they are susceptible or immune.

REFERENCES

1. Modigliani and deVilla: Pediatria **29**: 337, 1921.
2. Garzia: Pediatria **31**: 890, 1923.
3. Orgel: J. A. M. A. **79**: 1508, 1922.
4. Riesenfeld: J. A. M. A. **80**: 158, 1923.
5. Hull and Nauss: J. A. M. A. **80**: 1840, 1923.
6. Sauer: J. A. M. A. **100**: 239, 1933.

630 VINE STREET

A STUDY OF NEPHROSIS IN CHILDREN

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THE purpose of this paper is to emphasize certain facts concerning nephrosis, which we have observed in a careful study of several cases over extended periods of time. Only that literature having immediate relationship to our work is referred to, and no complete review is attempted. Fifteen patients have been admitted to the babies' wards of the New York Post-Graduate Hospital since 1915, and from this group we studied autopsies of three.

The nephroses fall into two main groups, as first proposed by Munk:[5] (1) Primary Nephrosis, corresponding to Munk's "Pure Nephrosis" and Epstein's "Lipoid Nephrosis"[1] and (2) Secondary Nephrosis.

Nephrosis is frequently classed with the chronic nephritic group, but infection of the kidneys, as shown by the usual kidney tests and urine cultures, is not an essential. It frequently occurs following tonsillitis, infectious sore throats, mastoiditis, and middle ear infections.

ETIOLOGY

Nephrosis is most commonly seen in chidren under five although no marked predominance as to age, sex, or locality exists. No organism has been found consistently as the causative factor, though the pneumococcus is frequently recovered. Stultz states that this organism has been recovered from the kidneys of his patients and is, in his opinion, the etiologic factor. We have recovered *Streptococcus viridans* and pneumococcus from the peritoneal fluid of the same patient (Case 1), and the staphylococci from several foci, i.e., mastoids, boils and middle ears. The predominance of evidence to date is in accord with our findings. It seems probable that there is a basic metabolic disturbance involving particularly the lipoids and proteins. The metabolic dysfunction alone is found in the primary type; in the secondary group, it is probably the predisposing factor for the subsequent infectious processes which produce the clinical symptom-complex nephrosis, namely, recurrent and persistent edema, high protein content in the urine, and absence of the urinary findings of nephritis.

From the Pediatric Department of the New York Post-Graduate Medical School and Hospital of Columbia University.

Laboratory work done at the New York Post-Graduate Laboratories.

SYMPTOMATOLOGY AND DIAGNOSIS

The symptoms of the present-day conception of nephrosis are quite universally recognized at the present time. The tendency of clinicians in the past has been to include under the classification nephrosis, cases which showed this symptom-complex, regardless of the laboratory and pathologic data.

Primary nephrosis usually has an insidious onset, presenting edema as the first sign of disturbed function. This frequently comes with no evidence of a preceding acute infection and may subside without the appearance of other symptoms. More commonly, however, it is followed by marked oliguria, lassitude, anorexia, and prostration.

In the acute stage, the patient may be afebrile, but a moderate elevation of temperature, pulse and respiration is more usual. During several relapses, we have observed vomiting and diarrhea; but in these instances the influence of diet and medication should be considered since neither symptom occurred constantly during the initial attacks. A common observation is the total disappearance and recurrence of the above symptom-complex without evident cause.

The laboratory findings are more constant. The urine examination reveals a large percentage of protein with a high concentration, the presence of double refracting crystals, and occasional hyaline casts. The blood proteins show a low albumin, a relatively high globulin, and a nearly normal fibrinogen content, with a decrease in the total protein percentage. This relative inversion of the serum-albumin to globulin ratio is considered to be characteristic. The lipoids are increased, especially the cholesterol and cholesterol esters. A cytologic count reveals a mild secondary anemia and frequently a moderate leucocytosis. In some cases, a lowered basal metabolism rate has been found but, due to the abnormal weight which includes an excess proportion of edema and a frequent lack of cooperation, metabolism was not seriously followed in our children.

CASE REPORTS

CASE 1.—A. P., male, three years and two months old, was first admitted to the hospital May 5, 1926, because of a persistent generalized edema which had been recurring periodically for the preceding ten months. Associated with the present attack, he has had moderate elevation of temperature (101°-102°), polyuria, anorexia, and malaise.

History.—Delivery was normal. At seven months he had several convulsive seizures, and at nine months, diphtheria, followed by bronchitis. Two months before admission he had a double middle ear infection with a persistent discharge from the left.

Family history was irrelevant.

Examination.—Examination revealed a boy, acutely ill and extremely edematous over entire body.

Head: There was purulent discharge from left ear; right drum was dull and retracted. Nasal mucosa was congested; tonsils large, cryptic, and inflamed; pharynx, red and edematous.

Neck: There was moderate adenitis with marked edema.

Chest: Heart was negative; blood pressure, 88/68; lungs, negative.

Abdomen: Ascites. Liver was enlarged and was two fingerbreadths below costal margin; spleen, not palpable.

Genitourinary: Edema of scrotum and prepuce.

Extremities: Edema.

Progress Notes and Treatment.—When first admitted, he was put on a low protein, salt-free diet, with restricted fluids. Circumcision and then meatotomy afforded local relief, but for a month there was no improvement except in these local conditions. Six weeks after admission, he was put on a high protein diet with thyroid extract (3 grains increased gradually to 10 daily) and given a blood transfusion. He showed fair response, but he did not become free of edema. He had measles in January, chickenpox in February, and mastoiditis in March, 1927; during each illness his condition became much worse, followed by a remission of symptoms. In August, 1927, he was practically free from edema and was sent to the convalescent home where a slight infection caused a return of the edema. In October, 1927, he developed pneumococcus peritonitis, and after a laparotomy and appendectomy, had a slow recovery. A tonsillectomy was performed in December, 1927, and after the removal of these foci, he had a period of comparative health from January, 1928, to April, 1929, when he developed normally on a regular diet and with hygienic living. In April, 1929, following a double otitis media, his symptoms recurred; while in the hospital, he developed streptococcus peritonitis. He died a few days later after an incision for drainage.

Laboratory Data.—Urine: Albumin—1 plus to 4 plus. Specific gravity—1.024 to 1.036. White blood cells—2 to 4 per high power field. Red blood cells—0 to 2 per high power field. Casts—none.

Phenolsulphonephthalein test: 16 per cent to 40 per cent in two hours.

Blood count: Hemoglobin 40 per cent to 85 per cent. Blood urea, blood calcium, and blood phosphates—normal. Serum albumin, 1.59; serum globulin, 4.02; and cholesterol, 0.16 to 0.420.

Pathology—

Kidneys: Gross: The left weighed 190 grams; the right, 185 grams. Both showed fine yellow mottling throughout. The structure was blurred; the cortex swollen to an average of 11 cm. with a translucent gray appearance sprinkled with yellow specks.

Microscopic: With hematoxylin-eosin stain, the kidney epithelium appeared swollen with vague outlines of the cytoplasm. The lumina of the tubuli were irregularly distended, and many contained amorphous granular material. The nuclear staining of the tubular epithelium was not always distinct. It had been lost altogether in many places. Most of the glomeruli were well-preserved. There were cellular streaks throughout the cortex where wandering cells were seen surrounding glomeruli, as well as the convoluted tubuli. Most of the wandering cells were polymorphonuclear leucocytes, but there were also a few lymphocytes. The glomeruli in these areas were quite cellular and also contained a few inflammatory cells—leucocytes and lymphocytes. There were also a few adhesions in the glomeruli, between the tufts and the capsules. The subscapular spaces showed edematous fluid and a few red blood cells. Other glomeruli showed some fibroblastic proliferation of the hilum. Freshly frozen sections under examination with the prism, showed the double refractile lipoid crystals abundantly in the tubular epithelium and calyces.

with a great deal of the fat in the convoluted tubuli as well. Under a prism the yellow streaks showed double refractile lipoid material.

Liver: There was a marked general infiltration of neutral fat throughout.

Thyroid: These sections were strikingly interesting in that there was practically no colloid material present.

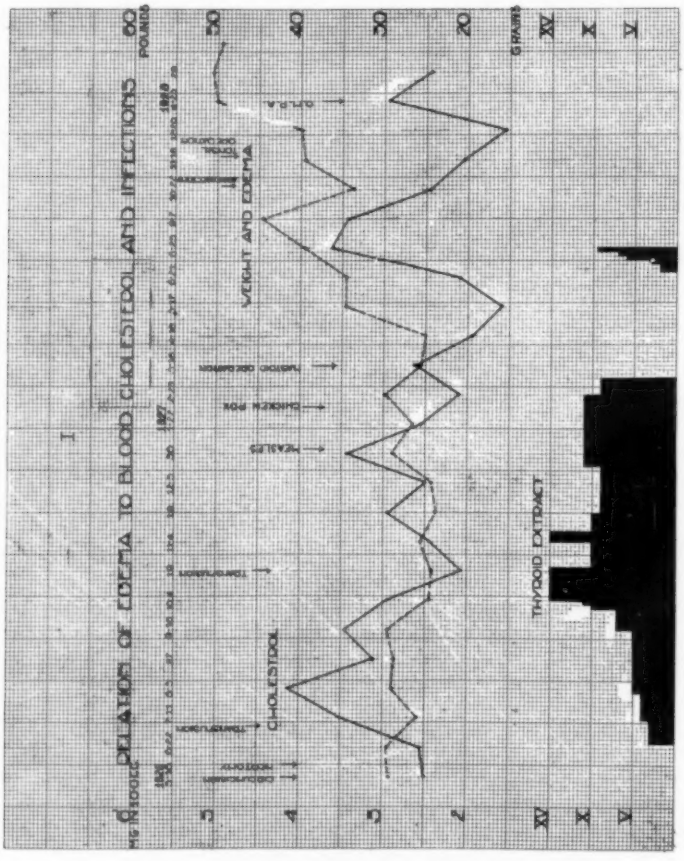

Chart 1.

The significant factors in this case which warrant a diagnosis of nephrosis are its typical clinical course, the repeated chemical blood analyses showing the usual changes, and the definite pathologic findings as revealed by postmortem examination.

There is a very striking relationship between the relapses and the presence of exciting factors. In this case, the exciting elements were the intercurrent infections or diseases. This relationship may be of value in determining the etiology of this much debated syndrome.

The dependence and relation of symptoms to blood changes is best demonstrated by following the points charted for weight and blood cholesterol (See Chart 1*). The most constant change was a loss of body fluids in the form of edema when the blood cholesterol rose above normal. The blood proteins were also studied but their fluctuations were not parallel with clinical changes to any important degree and did not uphold the studies of Barker and Kirk[20] and Shelburne and Egloff[21] which showed the development of edema concomitant with a lowering of the blood albumin content below 0.80 grams per 100 c.c. of blood. The effect of adequate dosage of thyroid medication on edema and nutrition was negligible. During the fourteen months he was free from illness and evident infection, he was to all appearances a normal boy.

CASE 2.—P. V., male, aged two years and six months, was admitted to the hospital July 2, 1928. Two and one-half weeks before admission the mother noticed a swelling of the face, especially under the eyes. This gradually spread to include the entire face, abdomen, legs, and feet. Three days before admission he had a generalized rash with fever, sweats, and malaise. For twenty-four hours he had been acutely ill and vomited once.

History.—Delivery was normal. In January, 1928, he was sick three weeks with pneumonia, but recovered without apparent sequelae.

Family history was negative.

Examination.—Examination revealed a boy, pale, acutely ill with a generalized maculopapular rash and edema, 4 plus.

Head: Eardrums were pink; tonsils large, but not inflamed.

Chest: Chest wall was edematous; both bases, dull; no râles; heart, negative.

Abdomen: Ascites, 4 plus with edema of walls.

Extremities: Edema, 4 plus.

Progress Notes and Treatment.—On admission he was treated as a potential acute nephritis patient with edema, but showed no improvement. He was then given low salt, high protein diet, with thyroid extract (¾ grains gradually increased to 9 daily) and various kidney and circulatory diuretics, but he did not respond favorably. During the first six weeks he had short periods of clinical improvement, but these showed no relationship to any specific treatment. During the seventh week his tonsils and adenoids were removed; following the operation he improved until he developed a furuncle. After this was drained, he improved again for a short period. At times he had marked intestinal upsets, accompanied by diarrhea, which decreased his edema but also weakened him considerably. He died four months after admission.

Laboratory Data.—Urine: Albumin—1 plus to 4 plus (.05 per cent to .31 per cent); specific gravity—1.012 to 1.030; white blood cells—5 to 10 per high power field; red blood cells—0 to 3 per high power field; casts—few hyaline.

Blood Count: Red blood cells—3.7 to 2.6 million; hemoglobin—50 per cent to 55 per cent; blood urea—9 to 49.9; blood calcium—7.2; blood phosphates—6.0. Serum albumin, serum globulin, cholesterol, see Chart 2.

*The peaks and low points are the points of observation. The connecting lines are to facilitate reading.

This case presents about the same course of events as the preceding one. The patient had a sudden onset with a gradually increasing severity of the symptoms following either acute diseases or local infections. The urinary findings, accompanied by a loss of blood proteins and an increase of cholesterins, are the diagnostic criteria of

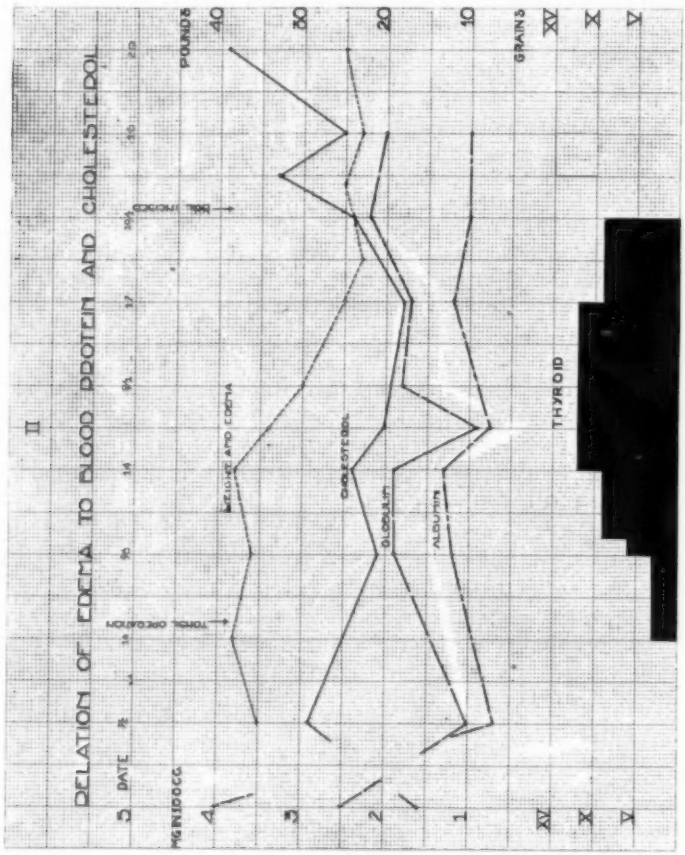

Chart 2.

importance. The clinical course and ineffectiveness of any medical treatment strongly support the diagnosis of nephrosis.

By following the course of this case on Chart 2, the most constant relationship is again seen to be the changes induced by infections, followed by the loss or gain of edema and the parallel increase or decrease in the blood cholesterins. The albumin and globulin content

showed an upward trend during one of the edematous periods; this is contradictory to the theory of blood protein loss as the cause of edema in nephrosis.

The effect of thyroid on edema in this case is not conclusive although the maximum dosage was associated with the one period of greatest improvement. On the other hand, this was not true at other periods during the course of the disease.

CASE 3.—L. B., female, aged two and one-half years, was admitted to the hospital May 8, 1929. Edema of eyelids developed February 15, and the urine at that time showed albumin, casts, and occasional pus cells. She responded to nephritic treatment, i.e., hot packs, diuretics, rest, and diet. On February 25, the condition recurred with generalized edema, anuria, anorexia, diarrhea, and vomiting. Treated at home for nephritis, she showed no improvement and was brought to the hospital in relatively the same condition.

History.—The patient had acute tonsillitis, January, 1928, and had had erysipelas at the age of three months.

Family history was negative.

Examination.—Examination revealed a well-developed and nourished child with generalized edema, pitting on pressure; temperature 101; pulse 136; and respiration 24.

Throat: Tonsils were large and red; mucous membranes of throat and pharynx, acutely inflamed.

Heart and Lungs: Normal.

Abdomen: Distended with fluid. There was a slight tenderness in lower half.

Extremities: Edematous.

Progress Notes and Treatment.—The edema decreased steadily after the first week, and the patient lost five pounds. In the third week, for no known cause, the swelling completely returned, but the patient remained apparently comfortable and had a good appetite. The output of urine was good. The edema disappeared and returned again with a mild bronchopneumonia on June 16. This time it was associated with anorexia and vomiting. For the third time, the symptoms cleared up and did not return in a month; consequently, the child was discharged on July 17. While at home, there were no edematous periods, but on August 15 she was readmitted in a much more serious condition than ever before. Following a tonsillectomy on September 1, she developed diarrhea and vomiting which resulted in edema and a transient loss of weight. On October 29, she had a left antrum infection, which was opened on November 4. The result was a marked improvement of symptoms and blood cholesterol. This change was credited partly to an accompanying erysipelas of the face, with its febrile reaction (103.5° F.). She remained comparatively free of edema from that time until February when she developed a peritonitis and died. Pneumococcus Group IV organisms were grown from the milky peritoneal fluid.

Laboratory Data.—Urine: Specific gravity—1.022 to 1.040; albumin—0.05 per cent to 0.73 per cent; red blood cells—occasionally white blood cells—5 to 20 per high power field; casts—hyaline.

Blood count: Red blood cells—2.5 to 3.9 million; white blood cells—7 to 24 thousand; hemoglobin—43 per cent to 85 per cent; blood calcium—8.9; blood phosphates—5.8; blood urea—20 to 43.2; blood proteins (see Chart 3).

Phenolsulphonephthalein test: 55 per cent.

Wassermann: Negative.

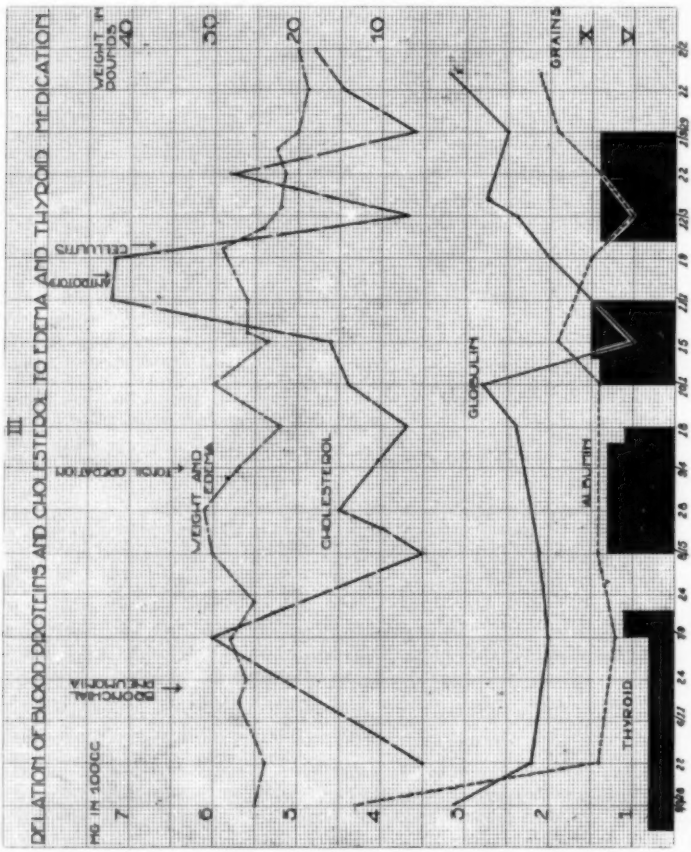

Chart 3.

The points of interest in this case are the extremely low blood proteins, which were below normal even when there was no edema, and the effect of infectious processes on the symptoms and blood cholesterol. During each illness, there was a rise in blood cholesterol and an increased edema, which was followed later by a remission. Thyroid medication had no noticeable effect. During the last two months, while she was doing well otherwise, a sudden attack of peritonitis caused death.

CASE 4.—J. H., male, aged eight years, was first admitted to the hospital on July 10, 1928. Previous to this admission, he had a cold, which was followed by swelling about both eyes. This improved under treatment but recurred shortly afterward with greater severity. He was removed from the hospital on August 2, 1928, and two days after, complained of dimness of vision. Later that day he had his first convulsion. During this period at home, he also had a marked diarrhea, six to nine stools daily. Headache persisted for one week. Second admission on August 22, 1928, was marked by coma and frequent clonic convulsions. The patient died thirty hours later.

Examination.—On first admission there was slight edema of face, forehead, skull, and the lower extremities, which pitted on pressure and returned slowly. His skin was pale.

Ears: There was an old, chronic, purulent otitis media of right ear with a very slight thin discharge.

Chest: Lungs were normal. Over the heart a soft systolic murmur was heard at the apex and transmitted to the axilla.

Progress.—In spite of all measures taken, he became continuously worse and died in evident uremic coma. Blood pressure taken at three-hour intervals was: 76/54, 80/62, 102/70, 108/68, 124/90, and 124/100.

Pathology—

Gross.—Liver: 785 gm. Friable with opaque yellow lobules.

Stomach: Hemorrhages of mucous membrane.

Pancreas: Hard.

Kidneys: Both large; left 175 gm., right 165 gm. Cortex was uniformly swollen, 12 mm. thick; edematous and gray in color with rich yellow striations. Pyramids showed a browned color.

Microscopic.—Spleen: Fibrotic changes shown, but no fatty deposits.

Liver: Marked histocytosis.

The kidneys showed a striking picture, especially around the periphery, where there were accumulations of large lipoid cells between the tubuli, and also some vacuolated cells. The glomeruli showed some adhesions between the capsules and tufts, but otherwise comparative freedom. Special stain showed large fatty deposits in the glomeruli, tubuli, and interstitial cells.

This case at first glance would appear to be an acute nephritis. The clinical course was unusual inasmuch as he had symptoms which would put him under both classifications, nephritis and nephrosis. The pathologic findings are quite conclusively those of nephrosis, with too few changes to account for his death by nephritis. The blood changes show the high cholesterol and lowered proteins with the inversion of the albumin to globulin ratio. In the treatment of his uremic symptoms, the usual measures were entirely ineffectual.

If this boy had lived, he would very likely have shown definite changes in the glomeruli and would be classed as a chronic glomeruli nephritis patient with a nephrotic component.

CASE 5.—P. J., male, aged three years and four months, was admitted to the hospital on April 20, 1928. On April 5, 1928, he had a sore throat with head cold,

followed next day by edema of the eyelids, legs, scrotum, pain in lumbar regions, and vomiting. Oliguria and hematuria followed for one week, with showers of purpuric spots on abdomen and extremities. Both patient's history and family history are negative.

Physical Examination.—Examination revealed large, cryptic, acutely reddened tonsils.

Kidneys: Palpable, but not tender.

Genitourinary: Phimosis.

Skin: Soft, light, with numerous small petechial spots on arms, legs, and abdomen. Moderate pitting edema of lower extremities and under eyes.

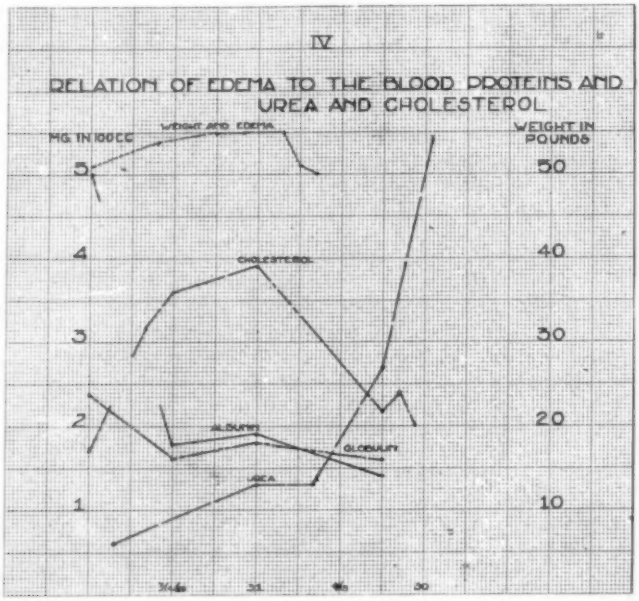

Chart 4.

Progress.—On April 27, he had a shower of petechiae with an accompanying increase in the hematuria and edema. On June 2, he received a blood transfusion; and on June 10, he had a third development of petechial spots. On June 25, his tonsils and adenoids were removed, but no improvement was noted. On July 30, multiple urethral strictures were found, and following their correction, he recovered and has had no recurrence to date.

This is an extremely interesting case, in view of the early removal of an evidently single etiologic factor, with a good result. It will be of great interest to see if subsequent disease in this case manifests itself in the symptom-complex resembling secondary nephrosis.

At the time of admission, the question of differential diagnosis presented itself. The purpuric spots, after clearing up, did not develop

following the tourniquet test. The platelet count of 328,000; bleeding time of five minutes and clotting time of six minutes were all against purpura hemorrhagica (the purpuras). Bloody urine is not the rule in nephrosis although the blood serums were greatly reduced and the cholesterol was increased. The generalized edema of the extremities

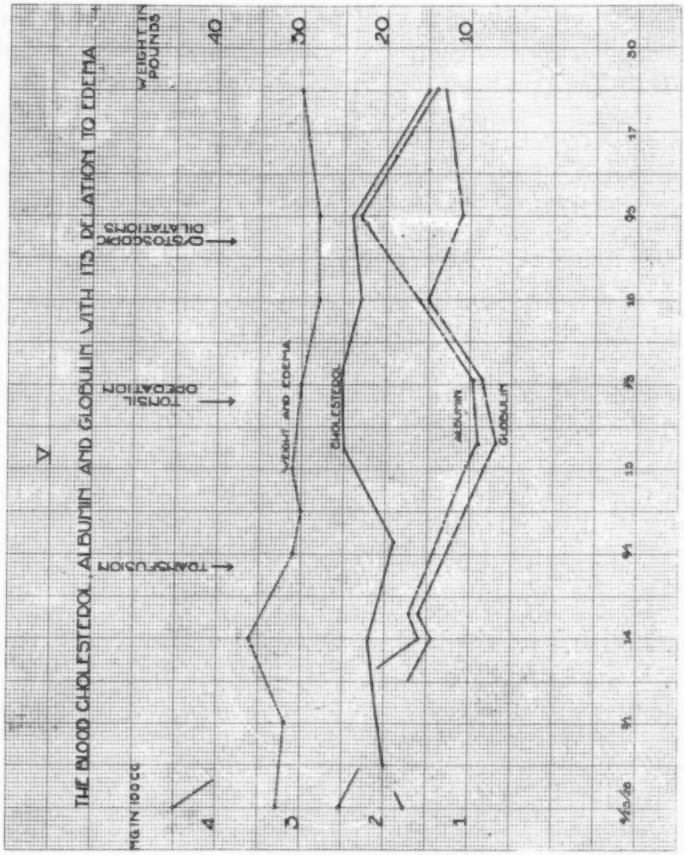

Chart 5.

and eyes was of transient character, not affected by treatment, and indicated the nephrosis.

This case is included here because it showed all the required laboratory and clinical changes. An entirely localized cause was corrected with a favorable response showing that the systemic disturbance causing these changes can be unbalanced by mechanical, as well as physiologic factors.

COURSE AND PATHOGENESIS

As demonstrated by the preceding cases, the course of this disease is very uncertain. The periods of improvement follow the patient's general condition rather than the individual factors of treatment and diet. This is in harmony with our concept of its etiology; namely, that there is a constantly predisposing element of metabolic dysfunction, and a variable element of resistance to infection. If easily accessible foci are present, their removal often leads to definite improvement, as was seen in Case 1, in which the patient had fifteen months of relatively normal health following a mastoidectomy; and in Case 5, in which after the removal of a mechanical obstruction, the patient is well to date. These patients are more vulnerable to infection, however, and each succeeding relapse seems to be worse. Aldrich[3] believes that most cases can be clinically cured if all such foci are removed, and considers them the major etiologic factor.

The course of primary nephrosis is variable, but those cases which successfully withstand the first attack usually progress to a chronic nephrosis. The others either succumb to the first attack or develop a subacute type and die from intercurrent diseases within a short time. During the remissions of chronic nephrosis, the patients seem to develop normally and to be in good health.

In the secondary types the course seems more dependent upon the severity and accessibility of the infectious elements. Even in those cases where foci are easily treated or removed, the eventual prognosis is not favorable.

Edema.—One of the outstanding features of nephrosis is the edema, which is generalized and pits on pressure with a slow symmetrical disappearance of the depression. There are several theories as to its cause and relationship to the disease. Lewis and DeScriver[16] suggest the disturbed calcium metabolism. Epstein[4, 22] believes it is due to a change in the osmotic pressure[2] exerted through a decrease of the blood serum colloids, i.e., serum, albumin, and globulin; and in his studies on edematous fluids, he found those in nephrosis low in this protein content. Munk[5] and Kollert, whom he quotes, believe the deficient serum-albumin and globulin exerts a hydrophilic power in the tissue cells while Elwyn[6] thinks it is a regulative process of the cells to prevent an increased blood volume. From our observations, we do not find this relation between the edema and blood proteins conclusive. Referring to the charts, periods of maximal diuresis are frequently seen when the protein content is the lowest, and also periods of greatest edema occur when the serum-albumin and globulin are increasing or nearly normal. (See charts.) Elwyn's hypothesis is supported by

Rowntree and Brown,[7] who found no increase in the blood volume during periods of edema in nephrosis. In the preceding cases, the most constant parallel changes were between the blood cholesterol and edema. (See charts.) The physiologic factors involved in this relationship are the distribution of the lecithin and cholesterin fractions in the cell membranes. Their normal ratio, as determined by Campbell,[9] is 2 to 1, lecithin to cholesterin. In diseases where the metabolism of fats is impaired and the cholesterol ratio increased out of proportion to the lecithin, there is a resulting change in the cellular constituents. This change of ratio alters the permeability of the cell membranes and acts in a hydrophilic manner to imbibe fluids, with a resulting edema. In normal people where a physiologic cholesteremia occurs, there are no symptoms; i.e., alimentary, seasonal, anemia, pregnancy, etc. In diabetes mellitus, where the fat metabolism is secondarily affected through the carbohydrates, the process is carried through to the fatty acid stage, and manifests itself by acidosis. In the more normal groups, infectious processes cause a decrease of blood cholesterol, while in nephrosis and diabetes, these metabolic deficiency products are greatly increased. This also explains the failure of the kidney and circulatory diuretics to decrease the edema, as well as the improvement following the fevers which are the result of infections.

Phenolsulphonephthalein recovery and a good range of specific gravity in the urine show that elimination by the kidneys is usually satisfactory.

The anemia is lower than the kidney function alone would account for,[19] and is probably due to the severe infections. It is of interest to note that the patient with the greatest gross loss of blood had the least infection and anemia. (See Chart 6.)

Cholesterol.—The cholesteremia is a result of the incomplete metabolism of fats. It is probably too high to be accounted for by a redistribution of the normal body cholesterol. We believe it plays a prominent part in the clinical course of the disease, as discussed under the pathogenesis of the edema.

Serum Proteins.—The low serum-albumin and globulin are caused by their loss through the urine. The more rapid regeneration of the globulin molecule[13] and the more rapid loss of the small albumin fraction, account for their inverted ratio. The fairly constant high fibrinogen content may have some part to play in the edema by influencing the osmotic pressure and increasing the total blood proteins.

Barker and Kirk[20] in their excellent study of plasmapheresis and the production of edema in dogs would put the point of edema formation at about 0.8 to 1 gram of albumin per 100 c.c. of blood and 3 per cent of total proteins. They produced both edema and kidney changes,

which they considered similar to those found in nephrosis, by this continual serum-protein depletion and were able to vary the condition as desired by the degree of proteinemia produced. The only factors which prevent these results from being compared to our clinical observations are the absence in the dogs of infectious processes that are so closely related to the whole process in humans and the hypercholesterolemia present in our cases.

In a thorough study of our charts we cannot confirm this protein point on the development of edema alone, because at times our pa-

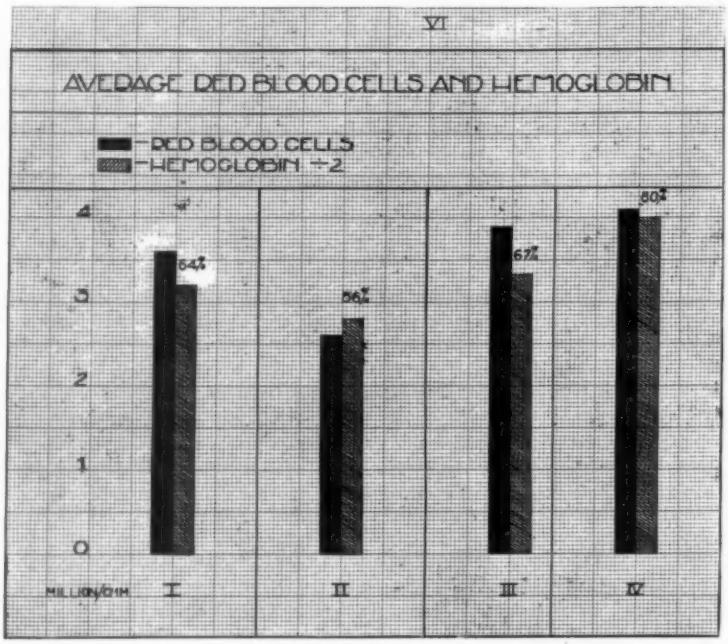

Chart 6.

tients were free from edema below this level and again had ascites when the albumin was well above 1 gram per 100 c.c. The continued edema without a return to normal of the plasma proteins is easily understood in these cases of nephrosis because the essential elements of edema are present, i.e., water and hydroscopic cholesterol or its components, even though a salt-free diet was adhered to constantly.

PATHOLOGY

The predominant feature of our cases throughout is extensive fatty degeneration. The kidney and liver are the most susceptible, and there we find the heaviest lipoidal deposits. Other viscera are also

involved—stomach, adrenals, and pancreas being most prominent. Inflammatory lesions were present in all of our cases, but generally seem more recent and less extensive than the degenerative ones. It is conceivable that the inflammatory lesions were superimposed on the degenerative lesions, which had predisposed the body to the disease processes. The lipoidal deposits in the kidneys are of interest. Their most frequent location was between the tubuli and in the interstitial cells. In many instances the glomeruli were free, and in some they showed evidence of secondary inflammation or degeneration. A detailed pathologic study is being made of these cases and will be reported later.

PROGNOSIS

From our cases, we can only conclude that the immediate prognosis is favorable in primary or early secondary nephroses. In the later cases of secondary type, the ultimate outcome is unfavorable. In our records for the past eight years, out of fifteen cases, one is now alive, and fourteen are dead.

TREATMENT

We are still in search of a dependable method of treatment for nephrosis. Various clinicians have followed individual methods, but none have been generally successful. Epstein[15] has shown good results on the high protein diet combined with thyroid extract or thyroxin, while Lewis and DeScriver[16] see improvement following parathyroid (Collip) medication.[11] Aldrich[3] believes that the removal of all infectious foci promises the best relief of symptoms and an opportunity for cure. We have tried many medical measures under well-controlled conditions and have found no single procedure to be constantly beneficial. Because of the metabolic nature of the disease, we started insulin therapy, but have had insufficient cases from which to draw any valid conclusions. Filligi[17] believes that insulin is indicated in any hypercholesteremia not physiologic in origin. From our experience with circulatory and kidney diuretics, we would class them in a group as ineffective to control nephrotic edema. The high protein diet seems to be of great benefit at times, but less effective in the secondary nephroses where infections are present. Epstein[15] accounts for its diuretic action through replenishment of the serum-proteins and stimulation of metabolism. King[18] believes a concentration of the blood urea where kidney efficiency is not seriously impaired, explains the diuresis following its use. This would explain the rapid fall of the blood cholesterol and edema after the onset of uremia in Case 4. It would seem that what benefit is derived, comes from the improved metabolism of fats, through the specific dynamic action of the protein. Certain protein foods have been tried by some clinicians over definite

periods in an attempt to determine which are the most efficient. The red and nucelar meats stand out as the best up to the present time. Nonspecific therapy has resulted in periods of transient improvement in some cases. Stock and homogeneous vaccines, antitoxin, milk, etc., have been used. Any benefit derived from these measures is probably the result of the febrile reaction, which usually followed the injections and caused an increased salt retention and consequent loss of fluids.

Our scheme of treatment is now as follows:

I. Hygienic
   A. Improved elimination.
   B. Bed rest.

II. Dietetic
   A. High protein; low salt in primary cases.
   B. Bland, low salt regular diet in secondary cases.

III. Medications
   A. Thyroid.[15]
   B. Insulin.

IV. Symptomatic
   A. Removal of focal infections.
   B. Transfusions of whole blood.

CONCLUSIONS

1. Nephrosis is a metabolic disease, accompanied by changes in the blood lipoids and proteins, and manifested pathologically by degenerative processes. Its etiology is obscure.

2. The edema is not directly of kidney or circulatory origin and is not entirely related in cause or effect to the blood-proteins. We believe it is of metabolic origin and follows, more or less directly, the blood lipoids and their metabolism with the resulting changes in tissue osmosis due to depleted proteins and increased cholesterol.

3. There is an accompanying anemia, which is out of proportion to the loss of kidney function.

4. The course of primary nephrosis may be favorably influenced for short periods by thyroid medication. Early secondary nephrosis is also similarly influenced by it, but only after all foci are removed.

5. The prognosis of primary nephrosis is unfavorable, as is that also of the secondary types, which result in chronic nephrosis. Secondary nephroses which develop into subacute or acute types usually result in early death.

6. The pathology is essentially that of lipoidal degeneration with a superimposed infectious element.

REFERENCES

1. Murphy, F. D., and Warfield, L. M.: Arch. Int. Med. **38**: 449, 1926.
2. Fishberg, E. H.: J. Biol. Chem. **81**: 205, 1929.
3. Aldrich, C. A.: Am. J. Dis. Child. **32**: 163, 1926.

4. Epstein, A. A.: Am. J. M. Sc. **154:** 638, 1917.
5. Munk, F.: Ztschr. f. klin. Med. **78:** 1, 1913.
6. Elwyn, H.: Arch. Int. Med. **38:** 346, 1926.
7. Brown, G. E., and Rowntree, L.: Arch. Int. Med. **41:** 44, 1928.
8. Murphy, F. D.: J. Clin. Investigation **5:** 63, 1927.
9. Campbell, J. H.: Quart. J. Med. **18:** 393, 1925.
10. Maxwell, J.: Quart. J. Med. **21:** 297, 1928.
11. McCann, Wm. S.: J. A. M. A. **90:** 249, 1928.
12. Fahr, G., and Swanson, W. W.: Arch. Int. Med. **38:** 510, 1926.
13. Whipple, G. H.: Am. J. Physiol. **47:** 356, 1918.
14. Epstein, A. A.: Arch. Int. Med. **36:** 563, 1922.
15. Epstein, A. A.: J. A. M. A. **87:** 913, 1926.
16. Lewis, D. S., and DeScriver, W. de M.: Ann. Int. Med. **2:** 66, 1928.
17. Filligi, G.: Ann. de Méd. **22:** 330, 1927.
18. King, E. S.: M. Clin. N. Amer. **10:** 963, 1927.
19. Ashe, Benj.: Arch. Int. Med. **44:** 506, 1929.
20. Barker, M. H., and Kirk, E. J.: Arch. Int. Med. **45:** 319, 1930.
21. Shelburne, S. A., and Egloff, W. C.: Arch. Int. Med. **48:** 51, 1931.
22. Epstein, A. A.: J. Exper. Med. **20:** 334, 1914.

33 E. Sixty-Eighth Street

A STUDY OF THE EFFECT OF PRESERVING METHODS ON HUMAN MILK

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THE studies here reported were conducted in cooperation with Dr. P. W. Emerson of the Directory of Mothers Milk, Inc., of Boston, Mass., and Dr. H. Shipstead of the Borden Company, to determine what method was most practical for handling human milk at a distribution service. The effect of dehydration and freezing on vitamin values was contrasted with liquid fresh collections. The dehydration method was developed by Dr. Shipstead.

The studies also afforded opportunity for contrast of the vitamin potency of these human milk supplies with those studies by other investigators, notably that of Dr. Icie G. Macy and collaborators[1] in Detroit.

A preliminary test of three lots of *dehydrated* human milk from the Boston Hospital showed considerable variability in vitamin A and vitamin B complex. Two of the lots averaged less than 70 U.S.P. units of vitamin A per oz. This third lot averaged about 180 units per oz. Sherman credits dried cow's milk with 500 units of vitamin A per oz., which would place these human milk specimens as decidedly poorer in vitamin A than average cow's milk.

Test for B-complex by the method of Sherman and Spohn[2] gave 28 units per oz. as against Sherman's 70 units per oz. for dried cow's milk.

In order to secure more comparable measurements, a fairly large amount of collected milk specimens were pooled. One part was dehydrated by the method of Shipstead and another part was frozen solid and kept in this condition until defrosted for feedings. As controls in A and G tests, market Grade A sample of cow's milk and shipments of fresh human milk were tested simultaneously. The latter obviously could not be pooled and represented day to day variations. Vitamin assays were then conducted on these products with the results noted.

VITAMIN A TESTS

Young rats from laboratory stock were placed at twenty-eight days of age on Sherman diet No. 379 and kept on this diet until free of

From the Laboratory of Physiological Chemistry in Teachers College, Columbia University, New York City.

stored vitamin A. They were then fed daily for a period of thirty-five days, equivalent amounts of milk, as determined by total solids. On the solids basis 0.4 gm. of dehydrated human milk was equivalent to 3.2 c.c. of liquid or defrosted milk. Chart 1 shows the result of the feeding tests after the clearing period.

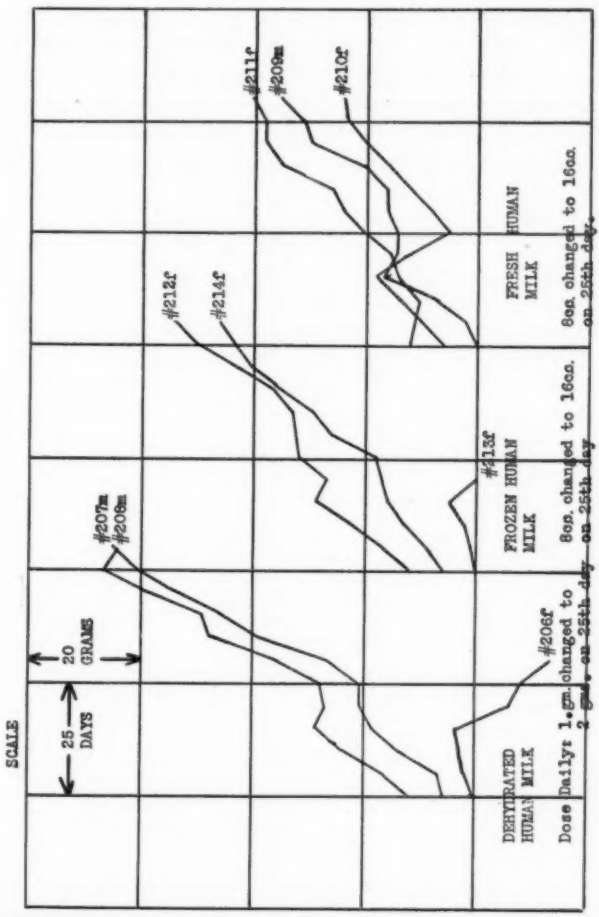

Chart 1.—The relative vitamin A potency of human milk after treatment by dehydration and freezing. The rats were first cleared of stored vitamin A by placing on Sherman diet No. 379. The effect of equivalent daily doses of three forms of human milk, fresh, frozen, and dehydrated, are shown. Freezing apparently resulted in less vitamin A destruction than dehydration.

In this series the dehydrated and frozen products were directly comparable, as they represented aliquots of the same pooled human milk specimens. The comparison was in favor of freezing as the better method of holding the vitamin A. The fresh human milk in this

series was shipped weekly from Boston and exhibited the variability already noted.

To check this test and also to establish some degree of comparison with cow's milk a second series was run, with the results shown in Table I. In this series the Grade A cow's milk was purchased weekly in the New York market.

This series confirmed the viewpoint that freezing is a preferable method of holding human milk if vitamin A retention is desired. It also indicated that the Boston milk specimens in this test were about the equivalent in Vitamin A potency to the 3.5 per cent butter fat, Grade A market milk as delivered in New York City, and certainly not superior to that in A content. (Table I.)

TABLE I

COMPARISON OF VITAMIN A POTENCY IN SPECIMENS OF HUMAN MILK AFTER VARYING TREATMENT WITH GRADE A MARKET COW'S MILK

(Daily dosage after clearing, 3.2 c.c. liquid milk or its equivalent)

TYPES OF MILK:	GRADE A COW'S MILK			FRESH HUMAN MILK	MELTED FROZEN HUMAN MILK	DEHYDRATED HUMAN MILK
Rats:	225f	221f	224m	222f	223f	220f
Days	gm.	gm.	gm.	gm.	gm.	gm.
0	80	105	94	95	89	96
5	83	83	98	105	85	95
10	88	98	111	116	110	103
15	107	113	124	129	123	113
20	120	124	148	142	145	127
25	135	136	162	157	156	141
30	135	145	165	161	160	147
35	140	152	181	166	167	150
Net gains:	60	47	87	71	78	54
Average:	65					

VITAMIN B TESTS

In this series the method of Chase and Sherman[3] was used to determine antineuritic potency, vitamin G or B_2 being supplied by B-free autoclaved yeast.

After clearing the stored vitamin B, tests were initiated with 1 gm. daily of dehydrated human milk against 8 c.c. daily of fresh and frozen milk. Later the daily dosages were doubled. The results are shown in Table II.

In this series dehydration apparently produced less destruction than freezing on vitamin B. If we take 3 gm. gain per week as the rate for unit B dosage, this rate was producible by 8 c.c. of liquid milk or 1 gm. of dehydrated milk daily. On this basis the B content of these human milk specimens appears to be 28 units per oz. of the dehydrated

product, about 60 units per pint or 120 units per quart. Comparative tests for Grade A cow's milk were not run. (Table II.)

TABLE II

COMPARISON OF VITAMIN B POTENCY IN VARIOUSLY TESTED HUMAN MILK SPECIMENS

TYPES OF MILK:	FRESH HUMAN MILK			FROZEN HUMAN MILK			DEHYDRATED HUMAN MILK		
Daily dose:	8 c.c.			8 c.c.			1.0 gm.		
Rats:	214f	212f	213f	209m	210f	211f	206f	207m	208m
Days									
0	52	55	40	46	63	52	53	52	48
5	55	60	41	48	67	51	55	53	53
10	59	66	42	53	71	50	56	60	60
15	62	72	45	62	75	54	57	65	65
20	63	70	40	59	69	55	47	67	63
25	64	75	died	59	62	60	45	67	64
Dose changes to	16 c.c. daily			16 c.c. daily			2 gm. daily		
30	72	68	–	61	65	64	40	73	72
35	75	76	–	61	69	66	died	85	84
40	81	79	–	65	73	75		92	85
45	86	86	–	75	77	78		100	95
50	89	93	–	76	80	78		107	103
55	92	97	–	80	81	80		111	100
Net change	40	42		34	18	28		59	52
Average	41			26				55	

TABLE III

COMPARATIVE VITAMIN G VALUES IN VARIOUSLY TREATED SPECIMENS OF HUMAN MILK

TYPES OF MILK:	FRESH HUMAN MILK		FROZEN HUMAN MILK		DEHYDRATED HUMAN MILK			GRADE A COW'S MILK	CONTROLS NO MILK
Rats:	227m	232m	234m	230m	228m	233m	231f	235m	229f
	Clearing Period								
Days									
0	62	55	53	65	47	55	54	55	56
5	63	61	56	71	48	61	56	64	60
10	60	64	60	69	50	62	61	67	63
15	65	62	62	75	53	62	68	68	68
20	71	73	72	78	54	72	70	77	74
	Test Period								
Daily:	5 c.c.		5 c.c.		0.6 gm.			5 c.c.	0.0 c.c.
25	80	79	76	86	61	76	72	85	77
30	91	84	76	88	62	78	83	98	80
35	95	91	85	90	67	82	81	108	65
40	103	94	90	97	74	90	90	120	68
45	112	100	100	108	80	98	98	133	65
50	122	99	101	109	82	105	103	141	63
55	132	111	111	120	83	116	114	156	died
60	144	117	119	127	87	124	120	167	
65	147	120	123	131	89	129	118	179	
70	156	120	124	129	87	131	125	190	
75	160	123	126	138	92	140	122	202	
80	168	122	128	147	92	145	125	212	
Net gains:	97	29	46	69	38	73	55	135	
Average:	63		58		55			135	

VITAMIN G TESTS

In this series the method of Bourquin and Sherman[4] was used, vitamin B being supplied by an alcohol extract of wheat germ. The first series of tests and their result is shown in Table III.

As was to be expected with this relatively stable vitamin little difference is noted between the G potencies of the dehydrated and frozen milk series. The series does, however, suggest a much greater paucity of G in human milk than in ordinary market cow's milk. To check this further, an additional series was run, using a daily dosage of 3 c.c. and comparing fresh human milk with Grade A cow's milk (New York market). These results are shown in Table IV.

TABLE IV

COMPARISON OF VITAMIN G VALUES IN HUMAN AND COW'S MILK

TYPES OF MILK:	FRESH HUMAN MILK				GRADE A COW'S MILK				CONTROLS		
Rats:	242m	244m	246f	248m	242f	245m	247m	249f	250m	252f	251m
					Clearing Period						
Days											
0	40	41	43	55	45	39	50	47	47	40	44
5	44	45	45	61	48	43	55	50	53	42	49
10	44	50	47	68	53	41	65	54	59	43	51
15	43	49	45	73	52	43	68	59	63	45	55
20	43	51	48	80	52	44	71	57	64	45	58
Test Period:	Daily dose except for controls 3 c.c. daily for human milk and 2 c.c. daily for cow's milk										
25	48	57	50	87	65	49	83	65	68	50	65
30	52	59	53	98	71	56	88	78	72	50	67
35	58	66	60	105	81	61	100	83	72	55	73
40	59	68	60	112	87	63	101	85	68	52	73
45	60	70	58	115	91	65	108	90	69	54	75
50	64	72	65	129	100	70	120	99	70	57	78
55	64	76	60	125	95	70	124	104	64	51	75
60	68	83	69	132	107	74	130	112	68	55	80
65	70	80	69	132	111	75	138	115	70	55	75
70	80	89	79	143	115	83	150	112	75	61	82
75	85	95	80	154	122	86	160	132	75	62	89
80	82	93	78	150	120	86	161	130	74	60	89
Net gains:	39	42	30	70	68	42	90	73	10	15	31
Average:	45				68				19		
Gain over controls	26				49						
Av. gain per wk. (over controls 3 gm.)					6 gm.						
Vitamin G Unit of Human Milk (Bourquin-Sherman) = 3 c.c. daily											

Donelson and Macy[5] measured the vitamin G content of pooled specimens of human milk in Detroit. They found 3 to 5 c.c. daily to be the amount necessary to maintain a continuous growth at the rate of 3 gm. per week, using the same method of assay employed by us.

Our tests, therefore, suggest that this G value is fairly general for human milk. Todhunter[6] reported the unitage of Grade A pasteurized cow's milk as about 21 per oz. It is evident from our test of Grade A milk that the unit was less than 2 c.c. (approximately 2 gm.), which would tend to confirm Todhunter's tests. On this basis our samples of human milk had about $\frac{3}{7}$ of the vitamin G value of ordinary New York City Grade A cow's milk.

VITAMIN C TEST

In order to arrive at any assay of human milk and not derange the consumption of adequate basal diet, the following plan was adopted:

Three control groups, one on basal alone, one on 1 c.c. of orange juice daily, and one on 2 c.c. of orange juice daily were provided. Previous experiments had established that the orange juice unit was from 1.5 to 2 c.c. for complete protection from scurvy. Against these, three groups were run, all of which received 1 c.c. of orange juice daily plus 25 c.c. of human milk or its equivalent (3.1 gm.) in the case of the dried product. It was believed that by this method any antiscorbutic potency in the milk woud be detectible. The results are shown in Table V.

Using either the growth curves or the autopsy scores as criteria, it is evident that the milk added little or nothing to the antiscorbutic content of the diets.

Human milk, therefore, resembles cow's milk in being an unreliable source of the antiscorbutic vitamin C. Granted that fact, its treatment during storage need not be considered of moment so far as effect on antiscorbutic potency is concerned.

VITAMIN D TESTS

The vitamin D, if present in milk, would be found in the butter fat, being like vitamin A fat-soluble. Using the method of Steenbock and his rickets-producing diet No. 2,965, rats were made rachitic on this diet and then fed during a ten-day test period measured amounts of human milk fat. The quantities tested were a total of 4 to 6 gm. in ten days. No better effect was obtainable with 29 gm. of the dried milk. The milk's content of D was therefore too small (if present) to be detected by these tests.

DISCUSSION

The primary object of these tests was to determine whether human milk collections could be preserved for distribution when needed by dehydration or freezing, without damage to their vitamin potency.

It would have been desirable to have used larger numbers of rats and guinea pigs in each test, but the amounts of milk available made

TABLE V

ATTEMPTS TO DETERMINE VITAMIN C POTENCY OF HUMAN MILK

DAILY DOSE OF ANTI-SCORBUTICS USED:	A. 1 C.C. ORANGE JUICE AND 25 C.C. FRESH MILK			B. 1 C.C. ORANGE JUICE AND 25 C.C. FROZEN MILK			C. 1 C.C. ORANGE JUICE AND 3.1 GM. DRIED MILK			D. NEGATIVE CONTROL		E. 1 C.C. ORANGE JUICE			F. 2 C.C. ORANGE JUICE	
Pigs:	453	454	455	456	457	458	450	451	452	462	463	459	460	461	19	20
Days 0	313	354	349	317	363	365	361	315	340	338	336	313	332	320	298	310
5	324	389	377	318	369	335	385	322	352	287	356	311	319	329	339	360
10	335	394	389	304	385	351	389	342	370	297	374	317	272	339	364	395
15	373	415	414	328	410	363	414	367	380	314	384	342	282	367	378	413
20	395	437	435	342	427	389	403	381	410	307	309	346	330	377	384	446
25	420	426	427	327	412	372	403	392	396	289	222	352	339	391	413	451
30	432	444	412	353	449	369	423	416	420	252	207	389	353	414	434	483
35	443	444	398	344	447	369	429	425	423	dead	dead	395	364	404	439	532
40	469	450	434	310	440	379	440	439	450			410	376	434	450	547
Net gains:	156	96	85	−7	77	14	79	124	110	−86	−129	97	44	114	152	237
Av. gain:	112			28			104			−107		85			195	
Autopsy Data																
Brittleness																
Bones	0	0	0	*	0	0	0	0	0	0	***	0	0	0	0	0
Jaws	0	0	*	0	*	0	0	0	0	**	***	0	0	0	0	0
Beaded Ribs	0	*	0	*	0	0	0	0	0	**	**	0	*	0	0	0
Hemorrhages																
Joints	*	0	*	*	0	*	0	0	0	*	**	*	0	*	0	0
Ribs	0	0	*	**	0	0	0	0	0	*	**	0	0	0	0	0
Muscles	*	0	0	**	0	0	0	0	0	*	**	0	0	0	0	0
Intestines	0	0	0	0	*	*	0	*	0	**	***	0	0	0	0	0
Gums	0	*	*	*	0	0	*	0	0	**	*	0	0	0	0	0
Score:	2	2	4	8	2	2	1	1	0	11	18	1	1	1	0	0
Av. Scores:	3			4			0.66			15		1			0	

this impossible. The findings are therefore not capable of being treated statistically. The present indications are subject to the limitations of our tests.

CONCLUSIONS

1. Freezing, in general, seems a very satisfactory method for holding human milk collections and does not appear to affect seriously the significant vitamin values (A, B, and G) in human milk.

2. Dehydration appeared to effect some destruction of vitamin A in our tests.

3. The samples of milk tested indicated the following potencies as representative.

   a. Vitamin A potency about that of Grade A New York market milk, unit less than 3 c.c. of liquid milk.
   b. Vitamin B potency, over 8 c.c. as the Sherman-Chase unit, 120 units per quart.
   c. Vitamin G potency was markedly less than that of Grade A cow's milk (New York City market); in this test not over 9 units per oz. as against about 21 units per oz. for the cow's milk.
   d. Vitamin C content not measurable, unit greater than 50 c.c.
   e. Vitamin D content not measurable, 6 gm. human milk fat not equal to a rat unit, A.D.M.A. standard.[7]

REFERENCES

1. Macy, I. G., Outhouse, Long, and Graham: J. Biol. Chem. **73**: 153, 1927.
2. Sherman, H. C., and Spohn, A.: J. Am. Chem. Soc. **45**: 2719, 1923.
3. Chase, E., and Sherman, H. C.: J. Am. Chem. Soc. **53**: 3506, 1931.
4. Bourquin, A., and Sherman, H. C.: J. Am. Chem. Soc. **53**: 3501, 1931.
5. Donelson, E., and Macy, I. G.: Am. J. Physiol. **100**: 420, 1932.
6. Todhunter, E. N.: J. Am. Dietet. **8**: 42, 1932.
7. Holmes, A. D.: J. Am. Pharma. A. **21**: 596, 1932.

RECOVERY FROM INFLUENZAL MENINGITIS

Case Report

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RECOVERY from the acute meningitis caused by Pfeiffer's bacillus is sufficiently uncommon to warrant notation of the circumstances under which the recovery occurs. A comprehensive review of the literature by Bloom[1] in 1930 disclosed a total of 24 instances of recovery from this disease, including one case observed by himself. Since this compilation, one recovery each has been reported by Martmer and Davidson,[2] Dabney,[3] in 1931, and by Johnson[4] in 1932, making a total of 27 instances of recovery from a total of approximately 400 cases of influenzal meningitis found in the available literature.

The present report is prompted by the observation of the apparently complete recovery of an eight-year-old boy who was one of four children with Pfeiffer bacillus meningitis admitted within the space of a month during the winter of 1932-33 to the Shreveport Charity Hospital, a state institution of 450 bed capacity.

REPORT OF CASE

History.—B. A. T., a white male, aged eight years, was admitted to the hospital on February 1, 1933, with the complaints of headache of twenty-four-hour duration and a convulsion which had occurred twelve hours before admission. There had been an acute coryza for several days before the onset of meningeal symptoms. Following the acute onset, fever and irritability were present and vomiting occurred several times during the day. Rigidity of the neck was noted during the night after the convulsion.

The past history was negative except for whooping cough at the age of two years, and the child had been in excellent health prior to the inception of the present illness.

General Examination.—The child showed normal development with no deformities and moderately good nutrition. He lay in bed in a right lateral position, with the neck dorsiflexed, the thighs flexed on the abdomen and the legs on the thighs. A fine macular rash was noted over the trunk and extremities. The pharynx was subacutely inflamed. The temperature was 100° F., the pulse rate 140 and the respiratory rate 30.

Neurological examination revealed the following abnormal findings: Kernig's sign, photophobia and stiff neck were present. The sensorium was clouded, the patient being occasionally semidelirious, irritable and restless, and unable to cooperate during the examination. There was an occasional left sixth nerve paralysis thought by us to be the result of increased intracranial pressure. The superficial reflexes were absent. The deep reflexes were slightly hyperactive.

Laboratory Examination.—The blood count showed: white cells 39,350 with 88

per cent neutrophiles, 9 per cent lymphocytes and 3 per cent monocytes; red cells 5,280,000; hemoglobin 85 per cent (Tallqvist). The spinal fluid was turbid, with cells too numerous to count; 78 per cent neutrophiles and 22 per cent lymphocytes; the globulin was increased and the Wassermann was negative. No microorganisms were found on the stained smear. Smears from spinal fluid taken on the second day showed Gram negative bacilli which had the morphology of Pfeiffer bacilli, with involution forms present. On two subsequent examinations of the spinal fluid, organisms apparently identical to those described above were found in small numbers. Several attempts to culture this organism on various media were unsuccessful.

Treatment and Course.—Before the organisms were definitely identified, treatment was instituted by spinal drainage twice daily and intraspinal administration of antimeningococcic serum once daily. This was carried out for four days, then spinal drainages were continued daily for a total of ten days, subsequently with sufficient frequency to maintain a normal intracranial tension (Table I). Rapid improvement was evidenced as soon as adequate spinal drainage was secured, and the clinical symptoms had practically subsided by the end of the second week. The manometric

TABLE I

SPINAL FLUID FINDINGS

DATE	MANOMETRIC PRESSURE IN CM. WATER	AMOUNT OF FLUID REMOVED IN C.C.	CELLS PER C.MM.	ORGANISMS
2/ 1/33		45*	Too many to count	No
2/ 2/33	260	35*	Too many to count	Present
2/ 3/33		25*	373	No
2/ 4/33		20*	1712	No
2/ 6/33	200	25	127	
2/ 7/33		18	67	
2/ 8/33	150	8	74	Few
2/ 9/33		15		
2/10/33	210	14	36	No
2/11/33	200	8	56	
2/13/33	110	10	36	
2/14/33	110	8	21	
2/15/33		8		
2/16/33	150	9	13	
2/17/33	155	8	18	
2/18/33	125	8	16	
2/19/33	135	8		
2/20/33	135	8	16	
2/21/33	135	8	40	
2/22/33	135	8	19	Occasional
2/23/33	120	10	12	
2/24/33	125	8	8	
2/27/33	100	5	17	
3/ 4/33	150	5	5	

*Two spinal drainages each day.

pressure had returned to normal about the fifteenth day of the illness and the spinal fluid cell count became normal on the twenty-fourth day. The patient was discharged as cured on the thirty-fifth day of the illness.

A letter from the patient's father on April 10, five weeks after discharge from the hospital, stated that the patient had been in excellent condition except for headache for one day soon after his return home, and slight stiffness of the legs. He was acutely ill with measles at the time the letter was written.

COMMENT

The age of this patient, eight years, is of interest in corroborating the previous finding that most of the recoveries from this disease occur in older children and adults, despite the fact, as shown by Rivers,[5] Ward and Fothergill,[6] and others that 75 to 80 per cent of the cases occur in children under two years of age. In Bloom's[1] tabulation of 24 recoveries, 17, or 71 per cent, of the patients were over two years of age.

In the treatment of this disease, as in all forms of nonmeningococcic acute meningitis, it appears that adequate drainage of the cerebrospinal fluid is the one essential. Apparently all of the individuals who have recovered have had repeated drainages of cerebrospinal fluid, although in many instances various sera and vaccines have been administered by different routes. Neal,[7] Abt and Tumpeer[8] and Bloom[1] were encouraged by results secured with antisera. Ward and Fothergill[6] considered an absence of complement as possibly responsible for failure from specific antiserum, and noted good response in five cases to combined treatment with specific antiserum and complement, although no recoveries followed.

More efficient drainage of the cerebrospinal fluid by laminectomy has been found valuable in one case of Pfeiffer's bacillus meningitis by Martmer and Davidson,[2] and in two cases of streptococcus meningitis by Leighton and Pringle.[9] Recovery followed in all three of these cases. Retan[10] advised the simultaneous intravenous injection of hypotonic sodium chloride solution, producing forced drainage through increased cerebrospinal fluid formation. The high mortality in all forms of nonepidemic meningitis should stimulate study of all measures which offer hope of success in treating these conditions.

SUMMARY

Apparently complete recovery from acute meningitis due to Pfeiffer's bacillus is reported in a boy eight years of age, following adequate spinal drainages.

Dr. W. H. Mathews and the hospital laboratory staff conducted the bacteriological study of this case.

REFERENCES

1. Bloom, C. J.: New Orleans M. & S. J. **83**: 455, 1931.
2. Martmer, E. E., and Davidson, E. C.: J. Mich. M. Soc. **30**: 936, 1931.
3. Dabney, V.: Laryngoscope **41**: 14, 1931.
4. Johnson, F. C.: J. M. Soc. New Jersey **29**: 311, 1932.
5. Rivers, T. M.: Am. J. Dis. Child. **23**: 102, 1922.
6. Ward, H. K., and Fothergill, L. D.: Am. J. Dis. Child. **43**: 873, 1932.
7. Neal, Josephine: Arch. Pediat. **38**: 1, 1921.
8. Abt, I. A., and Tumpeer, I. H.: Am. J. Dis. Child. **21**: 444, 1921.
9. Leighton, W. E., and Pringle, J.: J. A. M. A. **64**: 2054, 1915.
10. Retan, G. M.: New York State J. M. **31**: 1378, 1931.

MEDICAL ARTS BLDG.

TETANY OF THE NEWBORN

Case Report

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MEDICAL literature is rich in statements that tetany does not occur in the newborn infant. Many pediatricians fail to classify such a clinical entity. The following report is sufficient to add this apparently overlooked clinical phenomenon to a diagnostic armamentarium.

CASE REPORT

N. J. W. was born March 26, 1932, after a difficult delivery without instrumentation. He was apparently a normal infant having cried immediately after birth and at that time had no signs of intracranial pressure. At nine days of age, he began having generalized convulsions lasting approximately a minute at a time. These were associated with twitchings of both sides of the face. On this day there were two such attacks. From the following day until his fifteenth day of life the attacks occurred from seven to ten times a day. The doctor in attendance made a diagnosis of cerebral hemorrhage but did not make a lumbar puncture. On the fifteenth day I saw the child for the first time. The physical examination was negative except for a positive Chvostek sign on the left side. The child was admitted to Post Graduate Hospital with a tentative diagnosis of cerebral hemorrhage, or tetany of the newborn. A spinal tap was made, the report of which was negative. Fifteen c.c. of whole blood was given into each buttock in order not to delay treatment in case the chemical blood findings were negative. Blood for calcium and phosphorus was taken from the fontanel. Calcium bromide 2 grains was given every three hours. He had twenty-two generalized convulsions varying from thirty seconds to one and one-half minutes in length on this the first hospital day.

On the second hospital day he had fifty-two generalized convulsions the Chvostek sign remaining positive on the left side only. The convulsions varied from thirty seconds to seven minutes in length.

On the third hospital day he had thirty-three generalized convulsions varying from thirty seconds to three minutes, and the Chvostek sign remained positive. These were recorded up until 4 P.M. At this time the chemical blood analysis was reported, the calcium reading 7.3 mg. per 100 c.c. of blood and the phosphorus 4.4 mg. In view of the low calcium reading, one-half ampule (5 c.c.) of calcium gluconate was given intramuscularly, and the medication changed to calcium chloride —2 grains every three hours—and cod liver oil—15 drops three times a day. At 6:15 P.M., less than two hours after the intramuscular administration of the calcium gluconate, the child had one generalized convulsion lasting thirty seconds. From this time, the third hospital day, until the day of discharge on the eighth hospital day, there were no convulsions and the Chvostek sign disappeared the day after the intramuscular medication.

From the Department of Pediatrics, Post Graduate Medical School, Columbia University.

Two striking observations were that at no time did the child vomit and that evidences of hypertonicity were questionable. No carpopedal spasm was observed; no temperature at any time was noted. The calcium chloride was continued for ten days after discharge from the hospital, but the cod liver oil was gradually increased until at two months he was getting three teaspoonfuls a day. I have followed the child seeing him last at six months of age, and at that time he weighed 15 pounds 8 ounces. There has been no recurrence and he is in every way a normal baby for that age.

Bass[1] has covered the theoretical etiology of this symptom-complex. The striking factors in this case were the absence of marked tetanic symptoms, such as true spasticity and carpopedal spasm, and the rapid response to calcium medication. I think that any newborn child having convulsions when the spinal fluid is negative should have the therapeutic test of calcium administration, regardless of the lack of the more classical signs and symptoms of so-called tetany. Certainly no harm can be done.

The purpose of reporting this case is to emphasize that convulsions in the first few days of life may not be due to birth hemorrhage, that the symptom-complex, tetany of the newborn, does occur in the early days of life. Whenever there is doubt, the infant should be given the benefit of calcium medication.

REFERENCE

1. Bass, M. H., and Karelitz, S.: J. A. M. A. **97**: 1372, 1931.

12 East Eleventh Street

ANALYSIS OF SAMPLE DIETS AND DAILY HABITS OF 206 CHILDREN FROM DATA SUPPLIED BY PARENTS

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DURING the past two years sample diets have been collected from 206 children between the ages of two and eleven years inclusive. In all cases, the samples submitted have been lists of the total intake (solids and fluids) for a three-day period, translated into terms of simple measurement. Liquids have been measured in teaspoonfuls, tablespoonfuls, and ounces. Solids have been expressed, in the main, in heaping tablespoonfuls. Solid cuts of meat have been compared with the quantity of meat on a French lamb chop; and butter has been found easiest to express as "pats."

Originally, the estimations of intake were solicited as the most terse form of dietary discussion. They could be subjected to detailed examination for the inclusion of undesirable types of food and to caloric estimation. This was done, and both calories and food selections were then susceptible of easy comparison with a set of standard diets selected by the office. These standards were established with primary consideration for total available calories and their fractional distribution; and with secondary thought to supplying adequate minerals (calcium, phosphorus, et al.) and accessory food factors. The selections were made for this particular geographic area, from foodstuffs of fairly constant accessibility and uniform and moderate cost. They stand supplemented by Substitute Lists to ensure some degree of flexibility in deference to season, taste, and economic situation.

The requirements of infancy are regarded as a separate problem, and until the age of two years feeding remains a fairly individual matter. The Standard Diets, therefore, are designed to begin when the child is two years old and to guide feeding through the preadolescent period. There are daily menus for one week and yearly revisions of diets until the eighth birthday.

The requirements of the next six years are covered by two sets of diets. The three-year period of eight to eleven years has somewhat more generous allowances and varied selections.

The twelve to fifteen year standard may be considered a normal balanced adult diet which need not be detailed here. It was felt unnecessary to insist upon a systematized program for this age. For one thing, feeding habits would by this time be fairly well established.

For another, the child might logically expect a wider range and the inclusion of many "made" dishes, the exact caloric estimation of which is impossible.

Analysis of our standard diets from the standpoint of daily caloric provision and component protein, fat and carbohydrate follows:

TABLE I

ANALYSIS OF NORMAL STANDARD DIETS BY AGE

AGE IN YEARS	TOTAL CALORIES PER DAY	PERCENTAGE OF PROTEIN	PERCENTAGE OF FAT	PERCENTAGE OF CARBOHYDRATE
2	1251	16.7	35.7	47.6
3	1607	15.8	34.6	49.6
4	1667	16.8	34.1	50.1
5	1753	15.4	33.4	51.2
6	1826	15.7	34.4	50.9
7	1937	15.4	34.8	50.6
8-11	2470	15.8	34.8	50.6

Since most of the existent statistics on the feeding of children have been drawn from clinics and welfare centers it was recognized that this material might have value as representative of the situation in another group. Even at present little or no actual food shortage may be presumed to exist for the children attended by the pediatrician in private practice. The factor of economic necessity does not affect their dietary to any recognizable degree.

The situation is to be translated almost solely as an index of parental education in the field of dietetics for children.

TABLE II

ANALYSIS OF USUAL DIETS SUBMITTED FOR THREE-DAY PERIODS FROM 206 CHILDREN

NO. CASES	AGE IN YEARS	TOTAL CALORIES 24 HOURS	PERCENTAGE OF PROTEIN	PERCENTAGE OF FAT	PERCENTAGE OF CARBOHYDRATE
17	2	1247.7	16.7	29.6	53.6
27	3	1348.5	15.0	29.0	56.0
13	4	1467.1	15.7	35.1	49.1
23	5	1383.0	14.5	36.5	48.5
30	6	1585.0	14.5	34.8	50.3
26	7	1365.6	15.0	36.0	49.0
26	8	1797.2	16.7	39.0	43.6
12	9	1918.1	16.7	36.6	45.8
17	10	1656.0	16.2	37.6	44.3
15	11	1941.0	15.3	37.1	47.4

Analysis of the three-day dietaries submitted by mothers for 206 children, of whom 82 were boys and 124 were girls, demonstrated no consistent sex differences. Probably a sex difference does occur during the adolescent years when the growth spurt makes larger demands on food intake.

In this series the total caloric intake per day increases in rough proportion to age as may be seen in Table II. The proportions of protein, fat and carbohydrate are remarkably constant after the age of three years. The fat intake for the entire group is slightly higher than the usual textbook figure probably because of the tendency to overfeed slender-built children. This fact becomes apparent when the group is studied from the standpoint of body build.

This group of children showed a fairly normal distribution of body build. Twenty-four were classified linear type, eleven lateral type, and the rest intermediate type. The basis of classification was the width-length index of body build or relative breadth of the child. Children whose width-length indices varied more than one standard deviation below the mean for their age sex group were called linear, and those whose indices varied more than one standard deviation above the mean for their age sex group were called lateral. Means for age sex groups were based on 4560 children measured by us and distributed fairly evenly by age and sex.[1]

Examination of the three-day diets arranged according to body build of the children showed little difference in caloric intake per day for the different types of build at a given age. There was a marked tendency, however, for parents to administer a high proportion of fat food to their linear type children usually at the expense of the carbohydrate intake.

The averages of the three-day diets for all the linear and all the lateral type children contrasted is as follows:

AVERAGE PERCENTAGE INTAKE PER DAY

	PROTEIN	FAT	CARBOHYDRATE
Linear type	15.2	38.4	46.3
Lateral type	15.2	33.6	50.8

The 38.4 per cent fat intake for the linear type children is quite above the limits recommended by Holt,[2] McLean and Fales,[3] Aldrich[4] and other nutrition experts. The protein intake averaged exactly the same for both groups, while the carbohydrate supply was robbed to make up the high fat for the linear type group. Probably the high percentage of fat administered reflects the efforts of the mothers to fatten their slender-built children by giving high fat diets.

This corresponds to the findings reported by us in studying a group of children whose main complaint was anorexia.[5] At that time we found most of the hunger strikers were being forced to eat high fat diets and often quite contrary to their own desires. The previous study revealed the fact that in our office practice the children whose main complaint was anorexia were overwhelmingly (82 per cent) of slender body type.

At that time we began to treat anorexia with low fat diets and have had very satisfactory results.

Since then, finding how prevalent is this conscientious effort to fatten slender-built children by forcing extra cream, extra butter and rich foods, we have worked out special low fat diets for linear type children. Daily intake was calculated to supply 35-40 calories per pound body weight according to age. Protein, two-thirds of which was from animal sources, was planned to supply 15 to 16 per cent of the calories; fat 20 to 25 per cent; and carbohydrate, one-half sugar and one-half starch, 59 to 65 per cent. The diets were planned to supply an abundance of vitamins and minerals necessary for growth and development.

In addition to collecting information about usual diets we have also asked the mothers to report on children's daily habits and regime. The following form was used:

1. How much time does he take to eat his meals?
2. How much time does he spend washing and dressing?
3. What time does he rise in the morning?
4. Does he have a daily regular evacuation of his bowels?
5. How frequently during the day does he urinate?
6. How frequently during the night does he urinate?
7. Does he have a daily nap? How long?
8. Does he sleep quietly? Restlessly? Talk in his sleep?
9. During the day is he very active? moderately active? quiet? noisy?
10. Does he get tired? Greatly fatigued? Irritable?

An analysis of these questionnaires gives some interesting information. The preschool children averaged thirty-five minutes at each meal and the older ones twenty-two minutes. It took an average of twenty-six minutes for the preschool children to be washed and dressed, while the older ones required twenty minutes. Seven-thirty was the time when all the children got up in the morning. The two-year-olds urinated on an average of every one and one-half hours; the three-year-olds every one and three-fourths hours; the four- to six-year-olds every two hours, and older children every two or three hours.

The two- or three-year-old children had daily naps averaging one and three-eighths hours; the four- to six-year-olds napped one to one and one-half hours, and only an occasional older child took afternoon naps.

Three-fourths of all the children were reported as sleeping quietly. One-third of the preschool children were restless and talked in their sleep, while less than one-fifth of the older ones did.

Three-fourths of all the preschool children were described as active and noisy during the day and only one-fifth as quiet, whereas nearly half of the older children were described as quiet. More than half of all the children got tired at play, but only one-sixth showed great fatigue.

Less than one-third of the preschool children got irritable when tired, while half of the older ones were described as irritable when tired.

CONCLUSIONS

1. Three-day samples of the customary diet of 206 children aged two to eleven years were analyzed from the standpoint of total daily intake and distribution of the food elements.
2. No consistent sex differences were demonstrated.
3. Children of linear body build averaged a higher percentage of fat intake and a lower percentage of carbohydrate intake than children of lateral body build.
4. This supplements the previously reported observation that children whose main complaint was anorexia were preponderantly linear body types and were administered high fat diets.
5. Linear type children as well as those with anorexia profit by low fat diets.
6. Examination of daily habits and regime showed that three-fourths of all the children slept quietly. Those who were restless and talked in their sleep were largely in the preschool age group.
7. Less than one-third of the preschool children became irritable when tired, whereas irritability was reported on half of the older ones when tired.

REFERENCES

1. Pryor, H. B., and Stolz, H. R.: Determining Appropriate Weight for Body Build., J. PEDIAT. 3: 608, 1933.
2. Holt, L. E.: Care and Feeding of Children, New York, 1924, D. Appleton & Co.
3. McLean, S., and Fales, H.: Scientific Nutrition in Infancy and Childhood, Philadelphia, 1926, Lea & Febiger.
4. Aldrich, C. A.: Cultivating a Child's Appetite, New York, 1933, The McMillan Co.
5. Lucas, W. P., and Pryor, H. B.: Factors Involved in Combating the Hunger Strike in Children, Am. J. Dis. Child. 41: 241, 1931.

THE PROPHYLACTIC USE AND TOLERANCE OF HALIVER OIL WITH VIOSTEROL IN PREMATURE AND WEAKLING INFANTS

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THE halibut (hippoglossus) has been prized as a food delicacy for some time but only within the past year the halibut has come to play an important rôle in medicine. Apparently, the fact that its liver contains an oil that is far richer than the cod liver in vitamins A and D was overlooked until recently. The fish itself is one of the largest of the flat fish family, often measuring 5 feet from nose to tail and weighing from 100 to 200 pounds. The liver of the halibut is a comparatively small viscus, however, constituting only about 1 per cent of its body weight in contrast to the liver of the cod fish, which is approximately 5 per cent of its body weight. The liver of the halibut is capable of concentrating and storing the fat-soluble vitamins, vitamin A being resident in a higher concentration than D and both vitamins A and D, volume for volume of extracted liver, being one hundred times and twenty times greater, respectively, than contained in high-grade cod liver oil.

STANDARDIZATION OF HALIVER OIL

Emmett, Bird, Nielsen and Cannon[1] reported in 1932 a study of halibut liver oil with respect to its vitamin potency, physical constants and tolerance. These workers showed that the vitamin A potency per gram of oil ranged from 37,500 to 62,500 units with an average for thirty samples of 49,583 units, compared with cod liver oil standardized to 500 units per gram. Furthermore, the antirachitic vitamin D potency per gram of oil varied from 2,000 to 3,333 daily units, showing that the halibut liver is a much better natural source of vitamin D than cod liver oil. These workers found, also, that the physical constants, the specific gravity and saponification number of halibut liver oil, were essentially the same as for cod liver oil and that tolerance tests on rats gave no evidence of undesirable effects.

Following the preliminary laboratory studies of halibut liver oil, a clinical evaluation of the oil in various potencies of vitamin A in com-

This study was supported and all preparations furnished by Parke, Davis and Co., Detroit.

bination with viosterol 250 D was instituted. The dosage, growth-stimulating effect, antirachitic properties and tolerance, when given under properly controlled conditions to infants and children, appeared to be the phases of greatest investigative interest. Since the studies of Hess,[2] May[3] and others had conclusively proved the antirachitic value and tolerance of viosterol when given to premature infants in adequate dosage, it was believed that there was sufficient documentary evidence available to serve as comparison with groups of prematures and weaklings similarly treated with a high concentration of vitamin A in addition to vitamin D.

The information derived from observations on the use of halibut liver oil in various strengths of vitamin A combined with viosterol 250 D in forty premature and ten weakling infants forms the basis of this preliminary report.

OUTLINE OF PROCEDURE FOR STUDY

All infants studied were born in the maternity service of the Herman Kiefer Hospital. The majority of these babies were followed over periods varying from thirty to ninety days. Some were observed for longer periods and in a few cases the observation continued for a period of one year. The daily dose of haliver oil with viosterol was measured by uniform droppers delivering three drops to the minim. The dose began with six drops daily (one drop on the tongue before each feeding) and was increased gradually until maximal daily amounts of eighteen or twenty-four drops were being given. In a few cases, however, only nine or twelve drops were given daily. The haliver oil with viosterol used in this study was combined with different potencies of vitamin A derived from halibut liver oil and the dose was increased in accordance with the evident needs of each patient as indicated by the following laboratory and clinical criteria: (a) biweekly serum calcium and phosphorus estimations, (b) general growth and biweekly increase in weight, (c) persistence or improvement in craniotabes and monthly roentgenograms of the long bones, (d) complete blood counts monthly and biweekly hemoglobin determinations, and (e) appetite, well-being and sleep.

Breast feeding was followed in every possible instance, or, in lieu of it a complemental feeding was used when indicated, and formula feeding was resorted to when it became necessary to wean the infant. The formula feeding consisted of one part evaporated milk* and three parts boiled water with the addition of 6 per cent carbohydrate.†‡ All infants receiving artificial feeding were fed according

*Pet Brand evaporated milk was used throughout the entire study.

†Dextri-Maltose No. 1 was the carbohydrate used.

‡Borcherdt's Dri Malt Soup was used in conjunction with Dextri-Maltose in a few cases where there was any constipation.

TABLE II

OBSERVATIONS ON CHANGES IN WEIGHT, SERUM CALCIUM AND PHOSPHORUS BALANCE IN 25 PREMATURE INFANTS UNDER TREATMENT WITH VARYING CONCENTRATIONS OF VITAMIN A BELOW 30A DERIVED FROM HALIVER OIL COMBINED WITH VIOSTEROL 250D

KEY NO.	SEX	RACE	AGE (HOURS)	MAXIMUM DAILY DOSAGE (DROPS)	DURATION OF TREATMENT (WEEKS)	SERUM CALCIUM AND PHOSPHORUS (MG. PER 100 C.C.)				WEIGHT				REMARKS
						CALCIUM		PHOSPHORUS		BIRTH		GAIN		
						INITIAL	LAST	INITIAL	LAST	LB.	OZ.	LB.	OZ.	
1DF	♀	B	24	24	12	9.9	9.6	6.4	6.2	5	5	5	5	Breast fed.
2JT	♂	W	24	24	12	9.0	9.9	7.3	5.2	5	7	2	15	Formula fed. Influenza. Bilateral otitis media eighth week.
3MN	♀	B	24	24	6	8.8	8.2	6.5	7.1	4	11	1	4	Formula fed. Thymic hyperplasia.
4MH	♀	W	24	18	12	10.3	8.7	6.0	6.2	5	3	6	11	Breast fed.
5RC	♂	B	24	18	12	8.9	10.1	6.2	6.4	5	7	6	11	Breast fed.
6DP	♂	W	24	18	12	9.7	9.5	6.8	5.6	5	2	3	11	Breast fed. Thymic hyperplasia.
7JR	♂	W	24	18	12	8.9	9.6	6.9	5.6	5	6	5	14	Formula fed. Jaundice. Supportive treatment.
8BT	♀	B	24	18	12	9.0	9.9	7.0	5.4	4	5	5	6	Formula fed.
9EB	♀	W	24	18	12	8.1	10.6	6.8	6.0	4	6	4	10	Formula fed.
10AJ	♂	W	24	24	12	9.5	9.9	7.0	6.0	5	4	4	7	Formula fed.
11AT	♂	B	24	24	12	10.7	9.0	6.6	5.8	5	0	3	12	Formula fed. Thymic hyperplasia. Hydrocele.
12HD	♂	W	24	24	12	9.2	10.4	6.4	6.2	3	11	6	3	Formula fed. Twin. Supportive treatment.
13SA	♀	B	24	18	6	10.2	11.2	7.1	6.0	5	1	2	3	Formula fed.
14BG	♂	W	24	18	6	10.8	9.9	6.4	6.9	4	8	2	3	Formula fed.
15ER	♂	B	24	18	6	9.9	10.4	6.3	6.5	4	10	2	13	Breast fed. Thymic hyperplasia.
16CK	♂	W	24	24	6	9.6	9.2	6.8	6.0	4	8	1	1	Breast fed. Gavage fed. Supportive treatment.
17MP	♀	B	24	24	6	9.6	8.7	7.4	6.2	3	10	1	8	Formula fed. Lobar pneumonia.
18AM	♀	B	24	18	12	7.8	10.8	6.3	6.7	5	5	4	1	Breast fed.
19BK	♂	W	24	18	12	9.7	9.0	6.3	6.4	5	1	5	1	Formula fed. Thymic hyperplasia.
20GJ	♀	B	24	18	12	8.5	11.3	7.3	6.1	5	5	5	1	Formula fed.
21JT	♀	B	24	18	12	5.9	9.9	5.7	6.8	4	8	5	12	Breast fed. Diarrhea.
22BH	♀	B	24	24	12	9.2	8.9	7.0	5.9	4	8	4	8	Breast fed. Maternal syphilis.
23GS	♂	W	24	24	12	9.1	10.1	6.3	5.1	4	13	5	3	Breast fed.
24GC	♂	W	24	18	6	8.5	9.4	7.4	7.2	5	5	1	9	Formula fed.
25FR	♂	W	24	18	6	9.8	9.7	5.8	6.2	3	10	1	11	Breast and formula fed.

TABLE III

OBSERVATIONS ON CHANGES IN WEIGHT, SERUM CALCIUM AND PHOSPHORUS BALANCE IN 15 PREMATURE AND 10 WEAKLING INFANTS UNDER TREATMENT WITH VARYING CONCENTRATIONS OF VITAMIN A RANGING FROM 30A TO 60A DERIVED FROM HALIVER OIL COMBINED WITH VIOSTEROL 250D

KEY NO.	SEX	RACE	AGE (HOURS)	MAXIMUM DAILY DOSAGE (DROPS)	DURATION OF TREATMENT (WEEKS)	SERUM CALCIUM AND PHOSPHORUS (MG. PER 100 C.C.)				WEIGHT				REMARKS
						CALCIUM		PHOSPHORUS		BIRTH		GAIN		
						INITIAL	LAST	INITIAL	LAST	LB.	OZ.	LB.	OZ.	
1WW	♂	W	24	12	12	8.5	9.6	6.2	6.9	5	5	4	4	Formula fed.
2GMc	♀	W	24	24	12	7.0	9.5	5.9	6.4	4	11	3	2	Formula fed. Ophthalmia neonatorum. Gonorrheal vaginitis.
3DW	♀	B	24	12	18	9.8	9.6	7.6	5.8	5	11	6	0	Breast fed.
4RM	♂	B	24	12	16	11.3	9.3	6.5	5.6	5	11	8	13	Breast fed.
5JF	♂	B	24	24	14	8.4	10.1	7.4	5.8	5	13	6	11	Breast fed. Jaundice.
6JH	♂	B	24	12	10	8.9	9.2	6.8	6.1	5	9	4	15	Maternal syphilis. Formula fed.
7EL	♂	B	24	18	12	7.9	10.9	6.3	6.0	4	1	4	0	Formula fed. Umbilical and right inguinal hernia. Maternal syphilis.
8GC	♀	B	24	18	12	8.3	10.3	5.8	6.2	5	11	4	10	Breast fed.
9LJ	♂	B	24	18	6	10.2	10.1	6.4	6.2	5	14	2	15	Breast fed.
10HH	♂	B	24	18	4	10.1	9.4	6.4	7.4	5	9	2	5	Breast fed.
11AD	♂	B	24	18	10	9.6	9.9	5.9	5.1	5	15	6	13	Breast fed.
12ID	♀	B	24	6	8	10.0	9.6	6.0	5.4	5	15	4	3	Breast fed.
13EP	♀	W	24	6	12	9.0	9.9	6.0	5.9	5	8	5	11	Formula fed. Gavage fed.
14RC	♂	W	24	12	12	7.0	10.9	5.7	5.9	5	0	4	4	Formula fed. Gavage fed. Supportive treatment.
15LC	♀	B	24	18	12	8.7	11.0	6.1	6.8	5	1	6	4	Breast fed. Maternal syphilis.
16KF	♀	W	24	30	52	7.9	10.7	5.0	6.3	2	12	14	12	Formula fed. See case report.
17JL	♀	W	24	24	46	8.1	9.9	4.0	5.0	2	12	12	14	Formula fed. See case report.
18BL	♂	W	24	24	10	8.9	9.8	6.6	6.0	4	3	3	5	Formula fed. Jaundice.
19DN	♂	W	24	9	18	7.7	9.4	6.1	6.4	5	8	5	15	Formula fed. Twin.
20GN	♀	W	24	9	6	8.8	9.1	6.5	5.8	3	12	1	13	Formula fed. Twin.
21MW	♀	W	24	18	12	7.0	8.9	7.0	6.8	3	7	4	13	Formula fed. Gavage fed.
22AE	♂	B	24	18	20	7.0	7.9	8.4	5.4	5	6	9	5	Breast fed.
23GH	♀	W	24	12	26	8.4	9.6	7.2	6.2	4	12	9	1	Formula fed.
24BH	♂	W	24	24	52					4	12	20	0	Formula fed. See case report.
25BC	♀	B	24	24	12	9.5	10.1	6.0	5.8	5	14	5	14	Breast fed.

to the calory per pound of body weight and age method. Furthermore, orange juice was added to the diet at the end of the second week, fruit pulp (apple, prune or apricot) in the fourth month, vegetables, meat broth and zwiebach during the fifth month, and cereals during the sixth month for infants followed this length of time. All infants were vaccinated against smallpox before leaving the hospital.

The calcium estimations on the blood serum were made by the Tweedy modification of the Kramer and Tisdall method. Serum phosphorus was determined by the modified Fiske and Subarrow technic.

CLINICAL AND LABORATORY FEATURES

Classification of Infants.—In classifying the newborn infants as to their maturity, we divided them into the following groups: (1) abortion (living), (2) premature, (3) weakling and (4) full term. These groups are determined by three factors, namely: (1) weight, (2) length, and (3) fetal age. The approximates used for each are given in Table I.

TABLE I

BASIS FOR DETERMINING THE MATURITY OF INFANTS BORN IN THE MATERNITY DIVISION OF THE HERMAN KIEFER HOSPITAL

	FETAL AGE	WEIGHT	LENGTH
Abortion (living)	less than 28 weeks or less than 6½ calendar months	less than 1,590 grams or less than 3½ lb.	less than 35 cm. or less than 14 in.
Premature	28 to 38 weeks or 6½ to 8½ calendar months	less than 2,550 grams or less than 5 lb. 9 oz.	35 to 47 cm. or 14 to 18¾ in.
Weakling	38 to 40 weeks or 8½ to 9 calendar months	2,500 to 3,000 grams or 5½ to 6½ lb.	47 to 49 cm. or 18¾ to 19½ in.
Full term	39 to 40 weeks or 8¾ to 9 calendar months	over 2,700 grams or over 6 lb.	48 to 52 cm. or 19 to 20¾ in.

Ratio of Calcium to Phosphorus.—Notable fluctuations did not occur in the concentrations of serum calcium and phosphorus in the two groups of patients included in Tables II and III. The average serum calcium of the twenty-five prematures in Table II is 9.2 mg. per 100 c.c. of blood serum and the average serum phosphorus for the same group is 6.7 mg. per 100 c.c. at the beginning of treatment.

The average concentrations of serum calcium and serum phosphorus per 100 c.c. of blood serum for the subjects in Table III, consisting of ten weakling and fifteen premature infants, are 8.2 mg. and 6.3 mg. respectively, at the beginning of treatment.

Since the vitamin A potency was varied, ranging from 5A to 20A inclusive in the group reported in Table II and from 30A to 60A in the mixed series in Table III, the vitamin D remaining constant in its

concentration, such effects on the serum electrolytes as might depend upon the deprivation or excess of factor A might well become evident in a composite pattern derived from the biweekly quantitative determinations for each concentration of vitamin A.

The fifty patients, therefore, represented in Tables II and III, treated with the following dilutions of haliver oil: 5A, 10A, 20A, 30A, 50A and 60A, combined with viosterol 250 D, were segregated in their respective group for statistical purposes. In Chart 1 are represented the average level of serum calcium, serum phosphorus and the McCollum index for each group during a period of ten weeks' treatment.

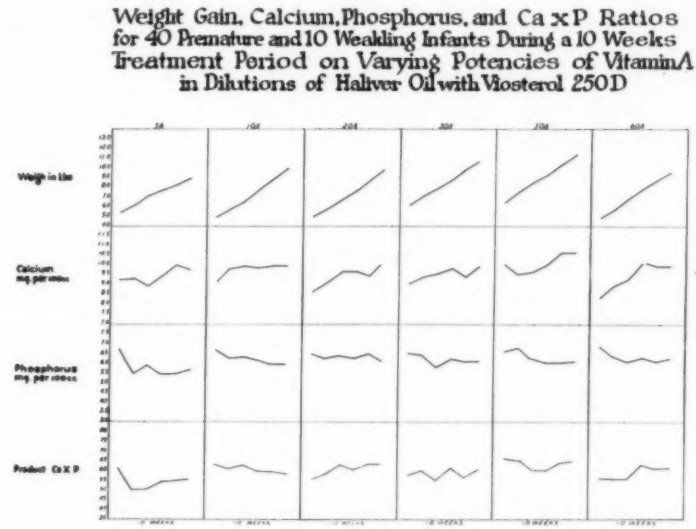
Weight Gain, Calcium, Phosphorus, and Ca x P Ratios
for 40 Premature and 10 Weakling Infants During a 10 Weeks
Treatment Period on Varying Potencies of Vitamin A
in Dilutions of Haliver Oil with Viosterol 250D

Chart 1.

There were only three subjects included in the series treated with the lowest dilution of haliver oil with viosterol. These three premature infants were not selected for treatment with this concentration because of any greater or lesser evidence of bodily vigor. It is evident, however, that their response to treatment, so far as the balance of serum calcium and phosphate is an index, was favorable throughout the entire period of ten weeks. The McCollum index of this group showed a decided drop at the end of two weeks' therapy but it was not at any time below a product of 40.

In the next higher dilution, 10A, there were fourteen premature infants. The serum calcium and serum phosphorus levels for this group during ten weeks' treatment showed less fluctuation than in the pre-

vious small group. The McCollum product remained slightly above or slightly below 60 throughout the course of the treatment period.

A third group of eight premature subjects was treated with haliver oil having vitamin A in a concentration of 20. It will be seen in Chart 1 that there was a definite increase in the concentration of serum calcium accompanied by a well-sustained level of serum phosphorus until the end of the eighth week. At this point the calcium rose sharply and the phosphorus decreased slightly. The McCollum index rose steadily, however, from 55 to 65.

Three distinct groups were treated with higher concentrations of vitamin A, namely 30A, 50A and 60A. The subjects in these three series were divided between premature and weakling infants. There were two premature subjects and four weaklings treated with 30A, one premature and five weaklings treated with 50A and twelve prematures and one weakling were given the 60A haliver oil with viosterol 250D accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

There is very little difference in the behavior of the serum calcium and phosphorus levels in the patients treated with the three higher dilutions. The calcium showed a trend toward a high normal with a consequent depression of the serum phosphorus, but the disparity between the two was not sufficiently great at any time to cause a remarkable change in McCollum's index. So far as these small groups indicate the effective dosage of vitamins A and D, it would seem that concentrations of 30A to 60A in combination with viosterol 250D are within a satisfactory therapeutic range. The inorganic elements seemed to be less mobile within the 5A to 20A range of dosage, hence it appears tentatively justifiable to assume that a vitamin A concentration above 20 in the haliver oil-viosterol combination is qualitatively and quantitatively adequate to control the two serum electrolytes under consideration.

WEIGHT GAINS AND GROWTH

The weight gain for each group of patients included in this series of fifty patients is presented in a composite graph, suitably designated in Chart 1. The average birth weight for each of the six groups varied within a narrow range, hence any disparity or uniformity in the response of the subjects to the varying dosages of vitamin A ought to appear in the comparative graphs.

Despite the fact that there was an unequal distribution of premature subjects and weaklings in the six groups, the former predominating in the aggregate as well as in each series, the average weight gain

exhibited by each group is similar. In a former section, it was pointed out that the groups treated with the lower dilutions of vitamin A: 5A, 10A, and 20A, showed less initial variation in their serum calcium and phosphorus levels during the early weeks of treatment than did the three groups receiving the vitamin A in the three higher concentrations. This datum cannot be correlated with the improvement in growth as measured by increase in bodily weight, however, since there was a dynamic change in weight from the first day of treatment in each of the six groups.

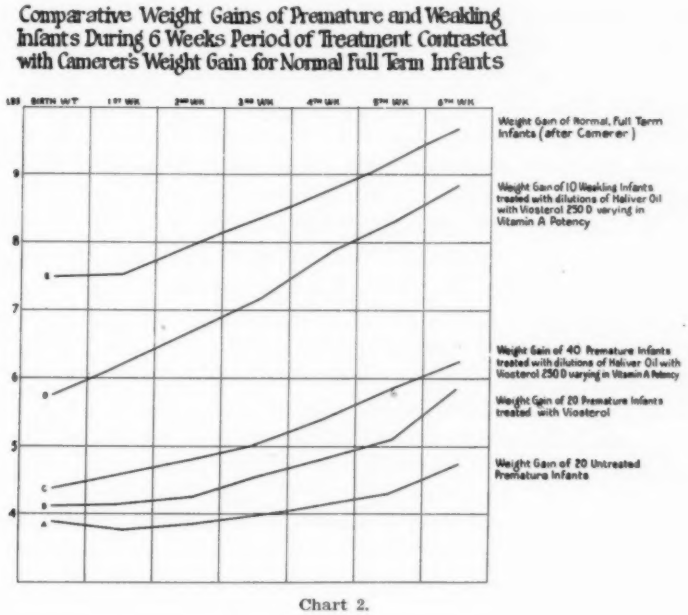
Comparative Weight Gains of Premature and Weakling Infants During 6 Weeks Period of Treatment Contrasted with Camerer's Weight Gain for Normal Full Term Infants
LBS
BIRTH WT
1ST WK
2ND WK
3RD WK
4TH WK
5TH WK
6TH WK
9
8
7
6
5
4
E
D
C
B
A
Weight Gain of Normal, Full Term Infants (after Camerer)
Weight Gain of 10 Weakling Infants treated with dilutions of Haliver Oil with Viosterol 250 D varying in Vitamin A Potency
Weight Gain of 40 Premature Infants treated with dilutions of Haliver Oil with Viosterol 250 D varying in Vitamin A Potency
Weight Gain of 20 Premature Infants treated with Viosterol
Weight Gain of 20 Untreated Premature Infants

Chart 2.

In order to show clearly that the improvement in weight for each of the six series of patients might or might not be influenced by the unequal numerical distribution of prematures and weaklings among the groups, Chart 2 was prepared. This chart includes weight graphs for three similar types of treated patients compared with an untreated group of prematures and Camerer's average weight gain for normal, full-term babies.

In Chart 2, Graph C represents the weight gain exhibited by the forty premature infants included in this report. Their average increase during a period of six weeks is 31 ounces. The ten weakling babies, composing the remainder of the fifty subjects in this investi-

gation, showed an average weight gain of 51 ounces. Camerer's normal full-term group (number unknown) gained 34 ounces as an average, hence the premature infants treated with haliver oil and viosterol 250D nearly equalled the growth recorded for full-term, healthy babies, while the treated weaklings exceeded the record for normals during the first six weeks of observation by 17 ounces, or 33.9 per cent greater improvement in growth when supplied vitamin A and D from an extrinsic source.

Inasmuch as there are available from a previous study of prematures by one of us (E. W. M.), data on their growth, both when treated with viosterol and without the addition of the vitamin preparation, a constant dietary regimen having been maintained throughout, these data are submitted in Chart 2, Graphs B and A respectively, for comparison with the subjects of this investigation. It will be seen that twenty prematures not treated by the addition of vitamins showed the lowest average weight gain of any group under consideration—14 ounces; whereas twenty prematures treated with viosterol for six weeks had an average weight gain of 28 ounces, or exactly 100 per cent improvement over the untreated patients. Furthermore, it is interesting that the viosterol-treated prematures had about the same average birth weight as that of the premature group in the present study. Their average gain, being 28 and 31 ounces respectively, was also proportionate. The percentage weight gain for each group cited in Chart 2 is given below. There was a notable similarity between the average birth weights of Groups A, B, and C. On the contrary, the weakling series, Graph D, was 30 ounces on an average below that of Camerer's full-term group, yet the weaklings showed a gain of 58.8 per cent in bodily weight in contrast with 28.3 per cent in the normals. The prematures from both series of studies showed percentage gains twice as great as the untreated premature group and appreciably greater than that of the normal, full-term infants.

	BIRTH WEIGHT (OUNCES)	WEIGHT AT SIX WEEKS (OUNCES)	NET GAIN (OUNCES)	PER CENT GAIN
Group A	62	76	14	22.5
Group B	66	94	28	42.4
Group C	70	101	31	44.2
Group D	90	143	53	58.8
Group E	120	154	34	28.3

ROENTGENOGRAPHIC AND CLINICAL EVIDENCE OF RICKETS

None of the infants in this series showed any roentgenographic evidence of rickets during the entire period of their observation except patient 17JL, Table III. The case history of this patient is given be-

low. Craniotabes was not found in any case nor were other signs of demineralization characteristic of rachitic changes detected.

Case Report.—Patient 17JL, Table III, was a seven-month premature female baby weighing 2 pounds 12 ounces. She was in poor condition at birth. Early evidence of cerebral hemorrhage appeared on the third day with slight twitchings and icterus. Early films of the chest showed areas of incomplete aëration. She was given supportive treatment of inhalations of carbon dioxide, 5 per cent, and oxygen, 95 per cent; interstitial saline; intramuscular whole blood injections and adrenalin injections during the first ten days, together with gavage feedings. For the next five weeks she improved definitely but about the sixth week her weight gain slowed up and her general condition was not good. Supportive treatment was again instituted. At the eighth week, the haliver oil with viosterol was discontinued for three weeks after which time it was continued. During this time, there was a steady improvement with complete recovery. The baby was discharged from the hospital on the one hundred and second day weighing 5 pounds 9 ounces. Roentgenograms at the end of the second month showed no evidence of rachitic change in the long bones. Studies on the serum calcium and phosphorus were not made until the end of the third month, which was at the end of the period of three weeks during which time she had not received any antirachitic treatment. The calcium and phosphorus ratio was 32.4, which was in the rachitic zone. This was also revealed by roentgenograms made of the long bones at this time. Two weeks later, the calcium and phosphorus ratio was 40.7 and in four weeks it was 66.0. Roentgenograms made at this time showed a definite healing of the rickets to be taking place. This prompt response of mineralization of the bones was very interesting. Each following study has indicated definite healing and the calcium and phosphorus ratio has been well within the antirachitic zone. At the age of eleven months the patient weighed 15 pounds and 10 ounces.

Dosage and Tolerance of Haliver Oil.—In the beginning, the dosage of haliver oil with viosterol was conservative. It will be seen in Tables II and III that several patients were given only 9 to 12 drops of the preparation daily. When it was found, however, that the haliver oil-viosterol combination was well tolerated, there being no gastrointestinal manifestations to indicate the contrary, the dosage of the various strengths was kept within a daily range of from 18 to 24 drops delivered from the standard pipette discharging three drops per minim.

So far as can be ascertained from this study, as measured by clinical and laboratory evidence, derived from roentgenology, blood chemistry, and studious observation, the optimal quantity of vitamins A and D required to prevent rickets in premature and weakling infants is not discernible. Even though the concentration of vitamin A was reduced to 10 and the dosage of the various concentrations varied, the evidence adduced for establishing an optimal requirement cannot be determined. Due to the fact that there were only three patients treated with the 5A preparation, this group has been disregarded in the foregoing comment on dosage.

GENERAL CONSIDERATION OF THE GROUP

The hemoglobin estimations were made on each patient in this series semimonthly. Fluctuations were found in the same degree, as is generally observed in rapidly growing normal infants. Such changes as occurred were not acute, and the same may be said of the red blood cell concentrations. Anemia was found in several of the subjects experiencing respiratory infections and other complications, but on the whole, the red blood elements were fairly well sustained throughout the period of supervision.

Appetite, sleep, and general constitutional improvement varied somewhat. Following discharge of these frail infants from the hospital, it is not to be expected that maternal care will always be ideal. Despite the shortcomings of home management, individually and collectively these premature and weakling infants showed very definite improvement in every respect, as would be deduced from their weight gains cited in a previous section of this report.

COMMENT

It is realized that there is some hazard in formulating conclusions based on limited observations and findings. That there was a necessity for establishing a dose range of a combination of viosterol with halibut liver oil, was recognized. Inasmuch as a preliminary period of nearly one year was devoted entirely to determining tolerance of the various types of oils submitted for clinical use, it is readily understood that the general investigation has been far more comprehensive than the substance of this communication implies.

Improvement in the physical character of the basic halibut liver oil has been accomplished with increasing experience in methods of extraction and purification. A word, too, is timely in respect to the simplicity of giving to immature and full-term infants additional amounts of natural vitamin A from this source. The small quantity required daily, 12 to 24 drops, given in divided doses before the regular feedings, is a practical method of administration. Furthermore, the small amount of tasteless oil is not disturbing to the babies; therefore, digestive upsets attributable to the medicament are negligible.

Acceptable proof of the importance of the various vitamins for the maintenance of health and well-being is not lacking. It would seem, also, that the prevention of rickets and the salutary effect of vitamins A and D on the growth of immature infants constitute acceptable evidence of their special merit in the care and management of human subjects born with a constitutional handicap. Admittedly, there may be some danger associated with too rapid development, hence it is not implied that all infants should be so treated as to double the rate

of growth established for normal full-term babies. The early attainment of a more robust physique in the case of premature and weakling infants is physiologically desirable; therefore, a cogent reason exists for giving this phase of infant nutrition critical attention.

REFERENCES

1. Emmett, A. D., Bird, O. D., Nielsen, C., and Cannon, H. J.: Indust. and Engin. Chem. **24**: 1073, 1932.
2. Hess, J. H., Poncher, H. G., Dale, M. L., and Klein, R. I.: J. A. M. A. 95: 316, 1930.
3. May, E. W.: J. A. M. A. **96**: 1376, 1931.

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A STUDY OF BREAST MILK FAT

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THE factors affecting the fat content of human milk have been studied extensively. Some of the factors are: period of lactation,[1] the breast from which the milk was taken,[2] the time of day the milk was obtained,[3] and the nationality of the lactating woman.[4, 5, 6] Perhaps the first work done on the composition of breast milk fat was by Ruppel.[7] Upon liberation of the fatty acids, he found a small portion which was water soluble, which probably contained formic acid, butyric acid, and caproic acid. The water-insoluble acids contained a mixture of oleic acid, myristic acid, palmitic acid, and stearic acid. Laves[8] analyzed breast milk fat and obtained the following composition:

One and four-tenths per cent volatile acids (as determined by the water-insoluble portion).

One and nine-tenths per cent water-soluble acids.

Forty-nine and four-tenths per cent unsaturated acids.

Butyric acid was present only in traces.

Caproic acid, caprylic acid, and capric acid were found in equal amounts.

Palmitic acid, stearic acid, oleic acid, and an acid of lower molecular weight, probably myristic acid, were also present in the nonvolatile acids.

A further analysis has been made by Arnold.[9] From two samples of fat, the following results were obtained:

Ninety-five and thirty-five hundredths per cent fatty acids.

Four-tenths per cent to 0.7 per cent water soluble.

Fifty per cent to 51 per cent oleic acid.

Forty-four per cent to 45 per cent water-insoluble, saturated acids with an approximate composition of 30 per cent palmitic acid and 13 per cent acids of the capric-lauric-myristic acid group.

The present investigation was made to determine further the fatty acid composition of the water-insoluble fatty acids found in breast milk fat. The milk, which was supplied by The Babies and Childrens Hospital, Cleveland, Ohio, was obtained from three subjects (A, B, and C) in different periods of lactation. Each sample was collected over a period of twenty-four hours. At the time the milk was taken A had been lactating fifteen months, twenty-two days; B had been lactating seven months; and C had been lactating nineteen months, eighteen days. Milk was obtained from the three subjects

From the Research Laboratory of S. M. A. Corporation, Cleveland, Ohio.

on three different days. In all but one or two cases, two analyses were made on each sample.

METHOD OF INVESTIGATION

The fresh milk was centrifuged until most of the fat separated. This was drawn off and the skim milk was centrifuged a second and third time. The fat was then extracted by the method of Mojonnier and Troy.[10] After saponification of the fat with alcoholic potash, the fatty acids were liberated with dilute acetic acid. The lead salt-ether method was then used to separate the solid and liquid acids. The two groups of lead salts were then treated with dilute mineral acid (hydrochloric acid for the soaps of the liquid acids, and nitric acid for the soaps of the solid acids). Whenever it was possible, the liquid acids were maintained in an ether solution until ready for use. Then upon evaporation of the ether, the last traces of ether were removed in the presence of hydrogen. This prevented any appreciable oxidation of the acids.

The solid acids contained a small amount of unsaturated acid, which was indicated by the iodine number. In order to lower the iodine value, the method of Twitchell[11] was applied, in which the lead soaps are precipitated in alcohol. After the iodine value was thus lowered, the solid acids were fractionally precipitated with magnesium chloride according to the method of Heintz.[12]

The liquid acids were brominated and the dibromide was separated from the tetrabromide by their difference of solubility in petroleum ether. The liquid acids contained a certain amount of the lower saturated acids. The iodine value of the liquid acids was about 80. Since the iodine value of the most common unsaturated acid (oleic acid) is 90.07, and since the sum of the per cents of the linoleic acid and oleic acid (the assumption is made that the dibromide is formed by oleic acid and that the tetrabromide is formed by linoleic acid) present in the bromides is less than 100 per cent of the original weight of the liquid acids, saturated acids must be present. The lead salts of caproic, caprylic, and capric acid, as well as a small amount of palmitic acid, are appreciably soluble in ether[13] which permits their passage into the liquid acid fraction. Corrections have been made for the amount of unsaturated acid in the solid acids and the amount of saturated acids in the liquid acids.

RESULTS

Since the physical and chemical constants of the breast milk fat samples were consistent with the values generally given, only a few values are listed.

	Fat Produced by		
	A	B	C
M. P.	33.5- 35.9° C.	36.5-38.9° C.	33.6-36.2° C.
Saponification Number	196.2-197.5	202.0	---
I-value	48.2- 49.6	46.6	50.3
Refractive Index 40° C.	1.4556	1.4578	1.4583
R. M. Number	2.67	2.33-2.84	---

The results include one specific analysis on fat produced by subject C on June 20, 1930. The water-insoluble fatty acids made up approximately 91 per cent of the fat. An average of fourteen different analyses is also given, representing fourteen different samples of breast milk fat from the milk of the three women.

	SUBJECT C	AVERAGE OF 14 ANALYSES
Percentage unsaponifiable material	1.47	1.52
LIQUID ACIDS		
Percentage of liquid acids in total acids	56.1	52.48
I-value of liquid acids	84.9	82.0
Percentage of oleic acid in liquid acids, as determined by bromine method	87.1	88.1
Percentage of linoleic acid in liquid acids as determined by bromine method	5.77	2.77
Percentage of lower saturated acids in total acids as given by the difference between the total amount of liquid acids and the sum of the amounts of oleic and linoleic acid times the percentage of liquid acids	4.00	4.79
Percentage of oleic acid in total acids	54.34	52.06
Percentage of linoleic acid in total acids	2.19	1.54
I-value of unsaturated acids corrected according to the proportion of oleic acid and linoleic acid present in liquid acids	95.55	92.66
Percentage unsaturated acids in total acids (correction made for amount of unsaturated acids in solid acids and for amount of saturated acids in liquid acids)	56.62	53.67
SOLID ACIDS		
Percentage of solid acids in total acids	41.5	46.9
Molecular weight of solid acids	256.0	259.9
Melting point of solid acids	49.6° C.	48.6° C.
I-value of solid acids	10.41	11.35
Percentage of unsaturated acids in solid acids with respect to total acids (found by dividing the I-number of solid acids by I-number of unsaturated acids and multiplying by the percentage of solid acids in total acids)	4.52	5.61
Percentage saturated acids in total acids (corrected for amount of unsaturated acids in solid acids and for saturated acids in liquor acids)	40.98	46.08
Percentage solid saturated acids	36.98	36.19

FURTHER INVESTIGATION OF THE SOLID SATURATED ACIDS

Two different samples of solid acids, having an I-value of approximately 10 were reprecipitated in alcohol with lead acetate. The following results were obtained after liberating the acids:

	I-VALUE	MOLECULAR WEIGHT	M. P.
Analysis I	4.2 -4.53	265	52.8° C.
Analysis II	2.92-3.23	262	51.7° C.

The iodine value was lowered and the melting point was raised. The molecular weight of a mixture of 70 per cent palmitic and 30 per cent stearic acid is 265. The melting point of the mixture is 54.85° C. Since the melting point of oleic acid is approximately 14° C., traces of the acid, as indicated by the I-value, lowers the melting point slightly, as indicated in the data which have been given. In

order to verify further this conclusion, the solid fatty acids with the low I-value were fractionally precipitated with magnesium chloride. Four fractions were obtained. In each case the acid was liberated and the molecular weight taken.

FRACTION	WT. OF ACID	MOLECULAR WEIGHT	STEARIC ACID	PALMITIC ACID
I	0.4546 g.	269	0.2109 g.	0.2437 g.
II	0.4629 g.	266	0.1653 g.	0.2976 g.
III	0.5264 g.	263	0.1316 g.	0.3948 g.
IV	0.4326 g.	257	0.0156 g.	0.4170 g.
Total acid	1.8765 g.		0.5234 g.	1.3531 g.
Percentage of stearic acid in solid acids			27.9	
Percentage of palmitic acid in solid acids			72.1	

In the case of the specific analysis of fat produced by subject C, the percentage of solid fatty acids was 41.5, or the amount of solid saturated acids was 36.98 per cent, and 27.9 per cent of 36.98 per cent is approximately 10.32 per cent, the amount of stearic acid in the total acids; 72.1 per cent of 36.98 is approximately 26.66 per cent, the amount of palmitic acid in the total acid. In a similar manner, the average of fourteen analyses would give 11.52 per cent stearic acid and 29.77 per cent palmitic acid.

CONCLUSIONS

From the analysis of the water-insoluble portion of the fatty acids obtained in fourteen different samples, the following approximate results were obtained. For the sake of comparison, figures for cow's milk fat (butter fat) are also included.[14]

	BREAST MILK FAT	COW'S MILK FAT
Amount of oleic acid	52.0%	27.0%
Amount of linoleic acid	1.5%	--
Amount of stearic acid	11.5%	11.0%
Amount of palmitic acid	30.0%	19.0%
Lower saturated acids	5.0%	43.0%

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REFERENCES

1. Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **10:** 229, 1915.
2. Myers, B.: Brit. J. Child. Dis. **24:** 249, 1927.
3. Plauchu, E., and Rendu, R.: Arch. de méd. d. enf. **14:** 582, 1911.
4. Skvertzov, V. I.: Amount of Fat in Human Milk, Russki vrach **11:** 1392, 1912.
5. Narobashi, D.: Ji. Kwa. Zasshi. No. **191:** 30, 1916.
6. Tso, E.: China M. J. **38:** 626, 1924.
7. Ruppel, W. G.: Ztschr. f. Biol. **31:** 1, 1894.
8. Laves, E.: Ztschr. f. physiol. Chem. **19:** 369, 1894.
9. Arnold, W.: Ztschr. f. Untersuch. d. Nahrungs-u. Genussmittel. **23:** 433, 1912.
10. Mojonnier and Troy: Technical Control of Dairy Products, ed. 1, p. 93.
11. Twitchell, E.: J. Ind. & Eng. Chem. **13:** 806, 1921.
12. Heintz, W.: J. pr. Chem. **66:** 1, 1855.
13. Neave, G. B.: Analyst **37:** 399, 1912.
14. Lewkowitsch, J.: Chemical Technology and Analysis of Oils, Fats and Waxes, ed. 6, Vol. II, p. 820, 1922.

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THE NIRVANOL TREATMENT OF CHOREA

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THE treatment of the chorea patient has long been a source of disappointment to the medical profession. We have had no means at our disposal for curing or shortening the usual course of this dreaded disease, especially in the more severe type of case. Rest in bed has been about as good a treatment as we possessed. As the result of our experience with the use of nirvanol, we feel we can attack the chorea problem with greater confidence of an early cure, even though the subsequent recurrence of this disease is not thus prevented. The treatment is not specific; but we cannot expect specific treatment as long as we do not know the specific cause of chorea.

Nirvanol was first employed in the treatment of chorea by Frieda Roeder[1] in 1919, and the first report on the subject in this country was by Kay and Cunningham[2] in 1930. Nirvanol is also known as phenylethylhydantoin and chemically is phenyl-ethyl-aceto-urea. It is usually administered in doses of from 0.3 gm. to 0.6 gm. daily. At Czerny's clinic in Berlin small doses are given t.i.d., and a rash is developed in about one week. Dennett[3] advised a tablet of 0.3 gm. t.i.d. to older children. One may also use the sodium salt of nirvanol hypodermically. As it is a barbital preparation untoward results may occur and, therefore, Hefter[4] advocated the hospitalization of chorea patients treated with nirvanol. Marick,[5] however, regards the home treatment with nirvanol as practical.

USUAL COURSE AFTER TREATMENT WITH NIRVANOL

The following is a typical course of a severe case of chorea after treatment with nirvanol.

C. D., female, six and one-half years old, was brought to the hospital with a very severe form of chorea. The aimless movements of her extremities were almost constant and very violent; her facial grimaces were markedly exaggerated; she looked dumb and did not utter a word from the time she entered the hospital until convalescence was established. She was unable to stand up or to feed herself. Bladder and bowel control were lost. After a few days in the hospital, a pseudo-paralysis of the left arm developed. She ran but slight fever, and her heart and urine were negative. The patient had been sick at home for about one week prior to her hospitalization.

The patient received three-fourths of a tablet of 0.3 gm. nirvanol b.i.d. and developed a mild morbilliform rash over the whole body and a rectal temperature of 100° F. on the ninth day of treatment. Three days prior to the appearance of the nirvanol rash the patient appeared worse than at the beginning of the treatment.

From the Children's Hospital, Pittsburgh, Pa.

On the day of her nirvanol reaction, i.e., the appearance of fever and rash, she seemed quieter. She continued to improve, and after two weeks, but slight choreiform movements of her extremities, and but slight weakness of her hand grip could be noted. It would be difficult to conceive such rapid improvement, in so short a time, in such a severe chorea case treated with the older methods.

The rash usually appears between the eighth day and the fourteenth day. It may be observed first on the limbs or on the body, and then it spreads over the greater part of the body. The face commonly escapes involvement. The mucous membranes may be somewhat injected. The rash resembles measles and the morbilliform rashes that sometimes follow the administration of certain coal-tar preparations. It is a toxic rash and hardly specific. The rash may be urticarial or resemble a severe dermatitis. A scarlatiniform, or punctiform, rash has not been observed in over sixty cases treated with nirvanol.

With severe reactions from nirvanol there may be marked conjunctivitis and swelling of the face and lips. Headache and vomiting are rarely present. The fever, which accompanies the rash, may mount as high as 104° F. or even higher. Usually, however, the fever is only several degrees above normal. The fever and rash last from four to five days, as a rule. We have seen it last ten days in one case. The rash may be afebrile. We have not observed fever without a rash after the nirvanol treatment. We have seen one case of chorea, treated with nirvanol, desquamate where there was no history or symptoms pointing to scarlet fever.

The nirvanol reaction is accompanied by changes in the blood picture. A leucopenia with an eosinophilia is usually present. Sometimes the eosinophilic count is quite high. There is present a tendency to a lymphocytosis.

UNUSUAL REACTIONS TO NIRVANOL

We have treated routinely, in hospital and private practice, over sixty cases of chorea with nirvanol without encountering any really serious reactions. We have also observed chorea cases similarly treated by others without untoward results. We are of the opinion that the nirvanol treatment of the chorea patient in the home is safe and practical and that hospitalization is not necessary.

Dennett stated that he had treated close to one hundred cases of chorea with nirvanol and had not seen any unfavorable results that could be attributed to the treatment. Some embarrassment occasionally follows the administration of drugs of the barbital group. If we compare chemically, nirvanol with luminal, we find that the former is phenyl-ethyl-aceto-urea, while the latter is phenyl-ethyl-malonyl-urea. Yet luminal, or phenobarbital, is used extensively both in the hospital and in the home. In our cases of chorea, only two showed an unusual

reaction. One child after treatment with nirvanol developed a severe dermatitis (nonpunctiform rash) with fever 105° F. The mucous membranes were inflamed and his skin looked somewhat swollen. His cardiovascular system and urine were negative. The fever and rash lasted seven days. His chorea subsided promptly. Another very mild chorea patient at the Belvedere Hospital received one tablet of nirvanol b.i.d. which made her very drowsy, but the treatment was continued for eight days when a rash developed. She remained more or less drowsy for about one week. Her rash was a severe generalized dermatitis. Her rectal temperature was 102° F. to 103° F. for three days then rose to 104° F. at which level it remained for seven days, touching 105° F. on one occasion. There was tenderness over the region of the liver and the spleen. She made a good recovery.

One chorea patient came in with a rash, which became aggravated during his first few days in the hospital. The administration of nirvanol was discontinued, and the rash promptly improved. We could not be certain whether or not it was the administration of nirvanol that had aggravated the existing rash. We have seen a morbilliform rash similar to that produced by nirvanol follow the prolonged administration of allonal tablets prescribed by a dentist for relief of toothache.

Hans Sehestedt[6] reported the case of an eight-year-old child convalescing from chorea after the nirvanol treatment, who some weeks later developed a "secondary reaction" or "nirvanol sickness." This child developed marked swelling of the face, eyes, lips, and mucous membranes. He had a badly coated tongue and appeared acutely ill. He made a good recovery. "Nirvanol sickness" appears after convalescence and is supposed by some to be allergic while others regard it as similar to serum sickness. It is also claimed that "nirvanol sickness" may be due to exposure of the patient to too much sunlight.

Keller[7] reported a case of "nirvanol sickness" with high fever, enlargement of the liver and spleen, jaundice, and bloody diarrhea. This case also recovered.

In this country Jones and Jacobs[8] reported three cases of chorea of long standing treated with nirvanol without improvement. One of their patients, a girl aged seventeen years, had acute articular rheumatism with mitral disease and epistaxis. After five days on nirvanol she developed a scarlatiniform rash and fever 102° F. Her blood showed no blood platelets for several days. Her epistaxis became worse and extensive hemorrhage into the skin and mucous membranes developed. Later she developed erythema multiforme. On one occasion there was cardiac embarrassment. Her chorea was not improved. Weinfeld and Cohen[9] have reported six cases of chorea treated with nirvanol without improvement.

In a preliminary report of the Council on Pharmacy and Chemistry[10] on the nirvanol treatment of chorea, it was stated that the treatment is too severe to justify its use except in those cases that do not yield readily to other treatment, and that nirvanol should not be used for the treatment of chorea except in an institution where the patient is under supervision. This report followed the publication of the article by Jones and Jacobs.[8]

As already stated, nirvanol is similar chemically and pharmacologically to luminal, and few would hesitate to prescribe luminal for use in the patient's home. Indeed, many people buy luminal over the drug-store counter.

In some cases failure to obtain improvement in chorea treated with nirvanol is seemingly due to insufficient dosage or to the fact that it was not employed long enough. Nirvanol is perhaps the best drug for chorea that we have at our command at present and we must realize that chorea is a serious disease and justifies the use of potent remedies.

TYPES WHERE BEST INDICATED

Nirvanol is, perhaps, best indicated in acute, infectious (rheumatic) chorea when it is severe or moderately severe. Judging from Jones' and Jacobs' experience, perhaps, it should not be used in the chronic forms of chorea, or where there is a very badly decompensated heart. Nirvanol can depress the formation of blood cells in the bone marrow according to Leichtentritt, Lengsfeld, and Silberberg.[11]

Furthermore, all children who twitch do not, necessarily, have chorea or, at least, rheumatic chorea. Children when overpressed with school work often become nervous and may exhibit marked facial grimaces. There may be twitching of an eye, or the nose, or the mouth, or the neck. These children are very emotional. They sometimes show awkward movements of the extremities. Such cases belong to the group of habit spasm or tic.

TYPHOID VACCINE FOR CHOREA

We have seen several cases of chorea treated with typhoid vaccine as advocated by Sutton.[12] The amount of shock following the injections as shown by chills, vomiting, severe headache, high fever, and marked prostration is a serious contraindication where there is already a badly damaged heart. We have observed several cases show prompt cessation of the chorea manifestations after the typhoid vaccine treatment. We feel, however, that nirvanol is a safer remedy, as it is free from shock.

ANALYSIS OF 55 CHOREA CASES

Sixty-two per cent of our patients were females; only two cases occurred among colored children. Thirty per cent were recurrent attacks of chorea, and one child had had five attacks. Only two cases

were concomitant with acute articular rheumatism; 31 per cent had a previous tonsillectomy; 47 per cent had an associated endocarditis while in the hospital. Only two failed to give a history of attacks of tonsillitis. Dental caries was exceedingly common.

RESULTS AFTER TREATMENT WITH NIRVANOL

After treatment with nirvanol 62 per cent of our chorea cases developed a rash between the sixth and fourteenth days. Some cases were treated over two weeks without a rash developing. Of those that developed a rash, some failed to develop a fever at about the same time. Yet, where a reaction after nirvanol failed to occur, improvement followed in some cases including severe ones. Schmall[13] has likewise reported cures where no primary reaction occurred. Possibly, we could have obtained more reactions if we had treated our chorea patients with larger dosages. It is probably correct that more striking improvement is noticed where there is a definite reaction with fever and rash, although neither is a sine qua non for improvement.

FOLLOW-UP OF CASES

We endeavored to follow up the cases of chorea treated with nirvanol during 1930 and 1931, in order to learn the frequency with which recurrences had occurred, and whether endocarditis had developed in those discharged with clinically normal hearts.

Some of the patients came in for an examination while others answered a questionnaire. Information was obtained from twenty-three out of forty-three cases chosen for study. In this small group 30 per cent had a recurrence of their chorea; 60 per cent claimed to have dyspnea on exertion; 33⅓ per cent regarded themselves still nervous. Two patients who had left the hospital without a diagnosis of endocarditis had since developed organic heart disease while two more patients had doubtful murmurs. We realize, of course, that our group is rather a small one. It is obvious, though, that nirvanol does not prevent a recurrence of chorea.

Although each of our chorea cases had a tonsillectomy prior to discharge from the hospital, the number of recurrent attacks was large. Several in the series had tonsillectomies a few years before their initial attacks of chorea. We believe that dental caries should be treated as soon as possible while the patient is still in the hospital. Many chorea patients are subject to head colds and should receive appropriate attention.

Acute articular rheumatism, chorea, endocarditis and untreated dental caries are associated with poverty, so that poor environment and inadequacy of food or vitamins must be considered in an endeavor to prevent subsequent recurrences of chorea. Whether such recur-

rences represent fresh infections or a recrudescence of some dormant infection is not definitely known, but the latter seemed the more likely. Since chorea is generally regarded as a rheumatic taint, the effect of a warm climate for children with chorea should be considered. We must endeavor to build up the patient's resistance to a maximum.

CONCLUSIONS

1. Nirvanol is a safe and efficient remedy for acute chorea. The usual dosage required is from 5 to 15 grains depending on age.

2. Nirvanol gives best results in the moderately severe and severe cases of acute chorea.

3. Nirvanol treatment does not prevent recurrences of chorea.

REFERENCES

1. Roeder, Frieda: Therap. Monatsh. **33**: 54, 1919.
2. Kay, Hartzel H., and Cunningham, J. S.: Am. J. Dis. Child. **39**: 1205, 1930.
3. Dennett, Roger H.: J. PEDIAT. **1**: 203, 1932.
4. Hefter, Elizabeth: Ztschr. f. Kinderh. **38**: 403, 1924.
5. Marick, S. W.: Arch. Pediat. **48**: 523, 1931.
6. Sehestedt, Hans: Deutsche med. Wchnschr. **55**: 740, 1929.
7. Keller, L.: Deutsche. med. Wchnschr. **54**: 1880, 1928.
8. Jones. T. Duckett, and Jacobs, John Lesh: J. A. M. A. **99**: 18, 1932.
9. Weinfeld, G. F., and Cohen, R.: J. PEDIAT. **1**: 210, 1932.
10. Preliminary Report of the Council on Pharmacy and Chemistry on Nirvanol: J. A. M. A. **99**: 33, 1932.
11. Leichtentritt, B., Lengsfeld, W., and Silberberg, M.: Jahrb. f. Kinderh. **122**: 12, 1928.
12. Sutton, Lucy P.: J. A. M. A. **97**: 299, 1931.
13. Schmall, S.: Deutsche med. Wchnschr. **35**: 1439, 1925.

CHRONIC SIALODOCHITIS

Recurrent, Alternating, Familial, Hereditary

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THE literature of this country and Europe fails to reveal many reported cases of chronic sialodochitis and those to which there is reference are of the parotid gland. Since I began the study of this patient, Londe and Pelz[1] have reported a résumé of chronic sialodochitis of the parotid gland, and the reader is referred to their paper for a study of the pathology and discussion of the cases. Burton-Fanning[2] has reported a case of "asthma" of Steno's duct, which is possibly of allergic origin.

V. C., aged six, of Italian-Irish descent, was first seen on Sept. 1, 1931. He complained of pain and swelling of the left side of the face. The mother stated that the child would become fretful, irritable, and restless. He would have a slight rise in temperature, loss of appetite, and the sputum would become ropy in character. The swelling would remain about ten days and then gradually subside, at which time the saliva would begin to return to normal. The mother further stated that the glands under the jaw would become involved, but that only one gland at a time would swell. However, on occasions when one subsided, another would begin to swell. The child had been sent home a number of times with the mumps.

History.—The boy had had mumps, pertussis, varicella, frequent colds, and growing pains. He has had diphtheria toxoid, smallpox vaccine, pertussis vaccine; and recently whole blood for prevention of measles. When a baby, he fell down and broke the lateral superior incisor.

He was a full-term infant. There was a normal delivery eighteen hours in duration.

He was breast fed for the first three months, then bottle fed. His diet was a well-balanced one prescribed by a pediatrician, but the family had made a feeding problem out of the child.

Family History.—Mother has had attacks similar to that of the child for the past twenty years; she has been under the care of an otolaryngologist with no relief, except that as she became older, the attacks became less frequent. The mother's grandmother had attacks similar to those of the mother and the child. The father is healthy and well. There are no other children and there were no miscarriages. There is no history of chronic, familial, or hereditary disease of which the family knows.

Examination.—The patient is a well-nourished white male, very cooperative and alert. He complained of pain and swelling of the left side of the face. The physical examination was essentially negative, except for the findings of the head and neck. The pharynx revealed a small amount of adenoid tissue on the posterior wall. The nasal mucous membrane was pale and exuded a watery discharge. The lateral

superior right incisor was broken at the junction of the middle and lower third. The left side of the face revealed a mass extending from the tragus to below the angle of the mandible and about one and one-half inches anteriorly. The mass was tense, firm and painful, but there was no change in color or temperature. When asked to open his mouth, the child would complain of pain in the region of the temporomandibular joint. The os of the duct of Steno on both right and left sides was pouting, but no pus exuded, nor could an increase in the flow of saliva be obtained when pressure was applied to the gland.

The laboratory report is as follows:

The first two smears and cultures taken from the duct showed mixed infection. The third showed only gram-positive diplococci resembling pneumococcus. The saliva was reported as being acid, but the figure of the P_H was not given. The blood chemistry was calcium, 11.8; phosphorus, 5.0; sugar, 81.5; urea, 14.3; N.P.N., 30.5. Three white counts were made. They are reported in order: (1) R.B.C., 4,850,000; W.B.C., 10,000; (2) hemoglobin, 78; R.B.C., 4,150,000; W.B.C., 16,500; polymorphonuclears, 63 per cent; small mononuclears 34 per cent; eosinophile cells, 3 per cent; (3) W.B.C., 6,400; polymorphonuclears, 45 per cent; small mononuclears, 55 per cent. The Mantoux and Wassermann tests were negative. A flat plate of the chest revealed slight hilus infiltration. A plate following lipiodol injection of the gland was read as dilatations of the minor ducts, and negative for stones. The urine was negative on three occasions.

Progress.—After this acute attack had subsided, the family was advised to test the saliva daily with litmus paper. Their report showed that it remained acid during the period of examination. The child was then put on an alkaline residual diet accompanied by large doses of alkalies. The reaction of the saliva changed to alkaline within three days and the gland began to recede immediately. On September 19, the alkalies were removed and the saliva showed an acid reaction. The recession of the gland ceased. The alkalies were added, and the gland then receded apparently to normal size. On October 25, the second attack occurred in the right parotid. The same procedure of therapy was carried out, except that the duct was not probed, and adrenalin was used to reduce the edema of the duct. The gland began to secrete, and the swelling and pain to subside. At the subsidence of right parotid, the left began to swell. The treatment was omitted to see if any results were being produced by therapy, or if it was merely a remission of the gland. However, after six days of watchful waiting, it was necessary to use adrenalin and alkalies to relieve the painful swelling. Whenever the alkalies were removed from the diet, the saliva immediately became acid, so an upset in metabolism was suspected. A carbon dioxide combining power was reported as 50 per cent. The report of a basal metabolism at this time was plus-minus. The Christmas holidays interfered with the experimental therapy as the child indulged in excessive play and eating. Chocolate was consumed in large quantities. During this time the child became languid, irritable, and lost his appetite. His breath became fetid, and a rash developed on his skin. This led me to think of the possibility of some allergic reaction, and the parents were advised that it was necessary to have the skin test made. This was delayed by an attack on Jan. 3, 1932, involving the left parotid. Lugol's solution was the only therapy used at this time. I observed that the amount of saliva excreted was increased, but that the size of the gland did not diminish to any great extent. After a period of six days, it was necessary to use alkalies and adrenalin to relieve the pain and tension. Following this attack the submaxillary glands became involved. This was relieved by alkalies and adrenalin. The patient's skin was tested during the week beginning Sept. 13, 1932, and was found to react to spinach, bacon, and paprica. Chocolate gave no reaction at all.

I was suspicious of this particular food so that it was eliminated from the diet along with the other three offenders. For the following eight months the child was free from all attacks unless we added the offending foods. Upon removal of these foods, relief was immediate. For the past three months, he has not had an attack. This is the first time in his span of life that he has had a good appetite, has gained steadily, has been full of energy, and has not complained of being tired and restless.

COMMENT

The interesting factors in this case are that it is familial and hereditary. The positive skin tests to certain foods suggest that it may be of allergic origin. I have no other history of the maternal grandmother except that she had similar attacks. The increase in the second W.B.C. was caused by an accompaning upper respiratory infection.

REFERENCE

1. Londe, S., and Pelz, M. D.: J. Pediat. 2: 594, 1933.
2. Burton-Fanning, F. W.: Brit. M. J. 2: 517, 1925.

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MALARIA IN THE NEWBORN

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THE mode of entry of malarial infection in the newborn has been a widely discussed subject in medical literature. In districts where the probability of transmission by the Anopheles is practically negligible, the mother is the only possible source of infection. Therefore, transmission may take place either by the transplacental route, or by placental separation during labor. The case of malaria here reported, in which the infant was given an injection of mother's blood soon after birth, offers an illustration of another mode of transmission of malaria in the newborn, infection by direct inoculation.

CASE REPORT

Baby N. G., aged nine weeks, was first seen March 12, 1931, suffering from what the mother described as "fainting spells and fever." During the previous ten days, the baby was seen in this condition at intervals of three days by the family physician, and at each examination the temperature was considerably elevated, 103-104° F. Observation during one of the so-called fainting spells revealed that there was no loss of consciousness. Instead, the baby was really in a state of apathy during which it refused breast feeding and continually whined. The skin became cold and pale and the mucous membranes had a bluish tint; all of which suggested a mild chill. After a number of hours, the patient became feverish and very restless. The frequency of the fever, and the enlarged spleen of the child, in addition to the fact that the mother had lived in Palestine, suggested the possibility of a quartan malaria. The child was removed to the hospital for further observation.

The patient's past history revealed the following: Both the father and mother were in a good state of health. The latter, a native of Palestine, emigrated to this country eight years ago. She disclaimed any knowledge of malarial infection. The infant, the first child, born at term, was delivered by forceps after a difficult and prolonged labor. The newborn was healthy and robust, and weighed 3,120 g. (6 pounds, 14 ounces). The baby was put to the breast after twenty-four hours, and nursed well, but on the third day became apathetic, limp, and drowsy. The resident physician, suspecting a hemorrhagic tendency, deemed it advisable to administer twenty c.c. of mother's whole blood intramuscularly. The next day the child was much better, nursed well, and gained weight. Two weeks later, the mother and child were discharged from the hospital in an apparently healthy condition. Up to the time of readmission to the hospital, the child had always been breast fed.

Temperature on readmission to the hospital on March 13, 1931, was 103.4° F. The physical examination showed the patient to be a well-developed, well-nourished, white male infant aged nine weeks, and weighing 4,890 g. (10 pounds, 12 ounces).

From the Pediatric Department, Mt. Sinai Hospital.

Respiration was rapid, the cry healthy and vigorous. The skin showed a miliary eruption over the upper abdomen. There was considerable anemia as evidenced by the pallor of the skin and mucous membranes. The mouth, throat, and ears were negative. The heart and lungs appeared normal. The abdomen was symmetrical with no dilated veins or visible peristalsis. The spleen felt hard and firm, and extended down to the iliac crest. The liver was palpable just below the costal margin. The extremities were negative, and reflexes normal. There was no evidence of rickets. With the possibility of malarial fever in mind, smears were made daily, and on the eighth day many organisms were found. The laboratory findings on admission were as follows: R.B.C., 3,420,000; W.B.C., 4,850; Hb, 55 per cent; polymorphonuclears, 14 per cent; small lymphocytes, 82 per cent; eosinophiles, 4 per cent. No nucleated R.B.C., no stippling, no anisocytosis, or poikilocytosis. Clotting time, 1½ minutes; bleeding time, 6 minutes. Platelets, 84,000. Fragility test, maximal resistance, 1.35 per cent; minimal, 0.55 per cent.

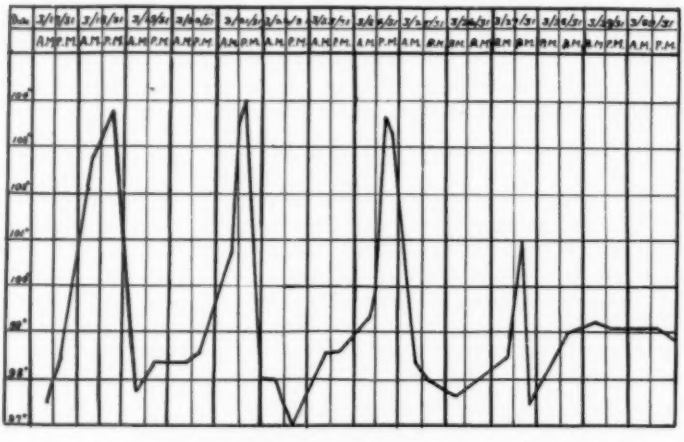

Chart 1.—Temperature chart of patient during his stay in the hospital.

The Widal test showed slight agglutination in dilutions of 1:40 and 1:80. No agglutination of para A or para B. Intracutaneous tuberculin test 1:1,000 was negative. Slide precipitation test and Wassermann test were negative. There were no growths in blood culture after four days. Stools showed no ova or parasites.

Urine was neutral in reaction, and contained no albumin or sugar. Test for benzidine was negative. Microscopic examinations showed an occasional white blood cell, but no casts.

In spite of the fact that the patient was running a temperature typical of quartan malaria, it was deemed advisable not to administer any medication before the finding of plasmodia in the blood. Upon discovery of parasites in the infant, a blood test of the mother was made, but revealed no plasmodia. Physical examination of the mother showed the spleen to extend one fingerbreadth below the costal margin. She refused to submit to further examination.

Quinine was given the patient in the form of cocoa-quinine in half-dram doses three times a day (three grains), but after six doses the amount was doubled and continued for eleven days until a total of seventy-two grains had been given.

On April 4, two days before discharge, the following was the blood picture: R.B.C., 4,250,000; Hb, 76 per cent; color index, 1. Polymorphonuclears, 29 per cent, small lymphocytes, 61 per cent; large mononuclears, 10 per cent. There were no anisocytosis, poikilocytosis, or malarial parasites present.

The child had four typical temperature elevations, seventy-two hours apart, the last one being on the tenth day of quinine treatment. The patient in a markedly improved condition was discharged from the hospital a week later. Further inquiry revealed that there was no recurrence of the fever.

COMMENT

The number of reports of malarial infection of the newborn from malarial as well as nonmalarial districts has been growing rapidly in the past few years. In 1922 Weselko[1] reports: "Of 200 newborn of malarial mothers, 187 were found to have estivo-autumnal parasites in the blood. Of these, 144 died in the first week, and twenty-eight in the second week." In 1924, Forbes[2] reviewed the literature on congenital malaria in nonmalarial districts and found twenty-nine cases. In the literature from 1924 to date, I have found record of 110 additional cases of malaria in the newborn.

It was not so long ago that the consensus of opinion was that malaria was not transmitted in utero. This belief was first strengthened by the work of Thayer[3] and many Greek and Italian investigators,[4, 5] who in lifelong studies in malarial districts had consistently negative results in searching for the malarial parasite in fetal blood, the cord blood and the fetal surface of the placenta. The fact that most of the cases which they observed appeared to be healthy and robust at birth with malarial symptoms entirely lacking, strengthened their conviction against intrauterine transmission. They therefore considered that malarial infection in the newborn was postnatal in origin or that in nonmalarial districts small areas of placental separation during labor may account for the infection of the fetus. Today, however, there is practically no doubt as to the possibility of transplacental transmission as is shown by the reports of Duschek,[6] Thibault,[7] Laffont,[8] Rabinoff,[9] Bass,[10] Hitte,[11] Dumollard and Viallet,[12] Adam,[13] Weselko,[1] Buckingham,[14] and others. Buckingham tells of two cases, which he saw in China, which clearly show that transmission was in utero. In one he found plasmodia in the child before the expulsion of the placenta. In the second case, fetal blood, obtained during the prolapse of the arm while preparing for delivery, showed malarial parasites. Hitte[11] investigated infantile malaria, demonstrated plasmodia in the umbilical vein in two cases. Weselko[1] reported fourteen cases in which he had six positive findings in blood smears from the placenta and four positive findings in smears from the fetal blood. Dumollard and Viallet[12] and Adam[13] found plasmodia in the cord blood and heart blood on the day of birth.

The author's own case presents a unique situation in which the infection may have been transmitted by the intramuscular injections of mother's whole blood. In this connection, as is well known, direct inoculation by transfusion has been employed in adults for treatment of central nervous system syphilis. Stein[15] reported a case where a father infected his two-and-a-half-year-old daughter by two transfusions. Recently, Jankelson[16] cited a case of malaria caused by a transfusion of father's blood, administered to an infant for the treatment of hemorrhagic disease of the newborn. In the case here reported, the blood was given intramuscularly. Although a review of the literature reveals no similar case, it is reasonable to assume that blood administered intramuscularly, could transmit the infection as well as blood administered intravenously. In fact, Nickum[17] has reported a case where a morphine addict contracted malaria from a small amount of blood in a hypodermic syringe used jointly with a friend who had malaria.

In spite of the fact that the mother was unaware of any malarial infection and the fact that we were unable to find plasmodia in her blood, she undoubtedly had a dormant malaria, contracted in her long residence in a malarial district, as is also evidenced by the finding of an enlargement of the spleen. Forbes'[2] review indicates that malaria in the mother does not have to be active to be transmitted.

It is to be noted, also, that the infant did not become ill until his seventh week like so many other cases of congenital malaria. The high degree of natural immunity possessed by the newborn for a short period after birth may explain this delay of symptoms.

SUMMARY

1. An unusual mode of malarial infection in the newborn is reported. In the case described, the infection was apparently initiated by the intramuscular injection of mother's blood.

2. Since the intramuscular injection of mother's blood is now a routine therapeutic measure, it is important to exclude the possibility of malarial infection in the mother donor.

REFERENCES

1. Weselko, O.: Ztschr. f. aertztl. Fortbild. **19:** 432, 1922.
2. Forbes, R. P.: Am. J. Dis. Child. **25:** 130, 1923.
3. Thayer, W. S.: "Lectures on the Malaria Fevers," New York, 1897, D. Appleton and Co.
4. Pezopoulos, N., and Cardamatis: Arch. de méd. d'enf. **10:** 29, 1907.
5. Marchiafava, E., and Bignami, A.: Twentieth Century Practice, New York, 1900, William Wood and Co.
6. Duschek, M.: Jahrb. f. Kinderh. **6:** 326, 1873.

7. Thibault, H.: J. Arkansas M. Soc. **12**: 243, 1916.
8. Laffont, A.: Paludisme Congénital et Paludisme Héréditaire, Paris, 1910.
9. Rabinoff, S.: Arch. Pediat. **37**: 494, 1920.
10. Bass, M. H.: Am. J. Obst. **69**: 735, 1914.
11. Hitte, L.: Le Paludisme Congénital, These de Montpellier, 1902.
12. Dumollard and Viallet: Bull. et mém. Soc. méd. d. hop. de Paris **26**: 229, 1909.
13. Adam: Bull. Soc. d'obst. et de gynéc. **13**: 181, 1924.
14. Buckingham, E. W.: China M. J. **39**: 1140, 1925.
15. Stein, H. B.: Am. J. Dis. Child. **44**: 1048, 1932.
16. Jankelson, I. R.: J. A. M. A. **97**: 177, 1931.
17. Nickum, O. C.: J. A. M. A. **100**: 1401, 1933.

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Pediatric Clinics

DEPARTMENT OF PEDIATRICS, COLLEGE OF MEDICINE UNIVERSITY OF CINCINNATI

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THE history of the Department of Pediatrics at the University of Cincinnati reflects, to a certain extent, the development and evolution of pediatrics itself. Considerably over a century ago in the Medical College of Ohio, the teaching of diseases of children was associated with obstetrics. Later it was connected with physiology. In 1895 it became a separate department under the leadership of Dr. Frederick Forcheimer, only to be combined two years later under the same professor with the teaching of the practice of medicine. In 1901 Dr. Benjamin Knox Rachford was appointed Professor of Diseases of Children and continued in this position when the Medical College of Ohio merged with the University of Cincinnati. Dr. E. W. Mitchell was appointed Professor of Pediatrics in the Miami Medical College in 1900 and occupied this chair until 1909 when the College merged with the Medical Department of the University of Cincinnati. In 1920 Dr. Kenneth D. Blackfan was appointed Professor of Pediatrics in the College of Medicine, University of Cincinnati, and occupied this position until his resignation in 1923 to accept the chair of Pediatrics at the Harvard Medical College. In the following year Dr. Harold Higgins was acting head of the Department until the appointment of the present incumbent in 1924.

The children's division of the Out-Patient Dispensary of the Medical College was established in 1880. The Children's Hospital of Cincinnati began its work in 1883 although it was not until much later that its medical work was affiliated with the Pediatric Department of the College of Medicine. In 1901 a pediatric ward service was organized in the Cincinnati General Hospital through the insistence and stimulation of Dr. Rachford. Here all infants and children were under the supervision of pediatricians no matter what their illness or injury.

Child welfare clinics in congested areas of the city were established in 1908. In 1920 Mrs. Mary E. Emery set up an endowment fund for the support of the Department of Pediatrics and the establishment of the B. K. Rachford Professorship.

The Children's Hospital, supported by the generous gifts of many citizens of Cincinnati under the leadership of William Cooper Procter, moved in 1926 to its new buildings adjacent to the College of Medicine. In 1928 Mr. Procter gave a generous sum of money for the establishment of the Children's Hospital Research Foundation. The Children's Hospital and its Research Foundation constitute the important unit upon which the Pediatric Department builds its functions.

In 1931 the Cincinnati Orphan Asylum reorganized its work, built its model Convalescent Home, and strengthened its connection with the Department of Pediatrics.

The child welfare work of the city, conducted by the Babies' Milk Fund Association, an agency affiliated with and supported by the Community Chest, has always been closely associated with the work of the Department of Pediatrics.

Gradually there have been developed affiliations and associations whereby many private agencies, as well as municipal, county, and social organizations, interested in the care of children have come under the direction of the Pediatric Department so far as their medical work is concerned, until much of the pediatric activities of the city radiate from the Pediatric Department.

ORGANIZATION

The Cincinnati Pediatric Clinic, if it could be so designated, is composed of the Department of Pediatrics of the College of Medicine, University of Cincinnati; the Pediatric Division of the Cincinnati General Hospital; the Contagious Disease Hospital of Cincinnati; the Children's Hospital of Cincinnati and its Research Foundation; the Convalescent Home of the Cincinnati Orphan Asylum; the Babies' Milk Fund Association with its welfare clinics; and the children's work in the Cincinnati Tuberculosis Sanatorium and Preventorium. In all of these organizations and institutions, as previously stated, the direction of the pediatric work is under the supervision of the Professor of Pediatrics, who holds the position of medical director of the several services mentioned. Allied and also under pediatric supervision is the work of the Nursery School conducted by the School of Household Administration in the University of Cincinnati, and special schools for delinquent boys and girls, which are part of the work of the Board of Education of Cincinnati.

The Children's Hospital is equipped to care for patients of any economic status and from any geographical locality. It has a capacity of 221, although some of the facilities have never been used. The average occupancy during 1932 was eighty-three. The house staff consists of one chief resident, seven assistant residents, and a dental interne.

The Pediatric Division of the Cincinnati General Hospital, which occupies a separate pavilion, has accommodations for approximately 100 infants and children, and during the year 1932 had an average daily occupancy of eighty. It receives only patients from indigent families of Cincinnati. The house staff consists of one chief resident, one assistant resident, and two internes. The Contagious Disease Hospital is the only institution in the city which admits children or adults suffering from acute contagious diseases. There are accommodations for 150 patients; however, the capacity can be increased during times of epidemics. There were 961 patients admitted to this service in 1932. The house staff consists of one chief resident, one assistant resident, and two internes.

The Children's Convalescent Home has facilities for 100 patients and admitted 260 children during 1932. Its resident physicians are supplied by rotation from the Children's Hospital.

The welfare work of the Babies' Milk Fund Association consists of five clinics situated in various thickly populated districts of the city. A total of 32,367 visits were made to the stations by 6,564 individual patients in 1932. In these clinics preventive pediatrics is particularly stressed.

In the several clinics mentioned there are organized special departments for the study and treatment of such conditions as diabetes, venereal diseases, heart disorders, allergic diseases, and behavior problems.

The Research Foundation of the Children's Hospital is housed in a separate building, which contains, in addition to the laboratory facilities, administrative offices, a library, a complete set of shops, a photographic unit, and animal quarters. Housed in this building with separate entrances is an Out-Patient Clinic so physically equipped that there is no contact between patients from the time of entrance to the clinic until the visit is over. The Research Foundation in its studies utilizes all the affiliated institutions and organizations of the Pediatric Department. It is

under the direction of the Professor of Pediatrics and under the immediate supervision of the Director of Laboratories, who is also the Professor of Research Pediatrics in the College of Medicine.

STAFF

The clinical staff is composed of four groups: the so-called full-time pediatricians; part-time physicians; physicians on a voluntary basis, who receive no salary; and the resident group, a number of whom are graduate students enrolled in the Graduate School of the university. The definition of full-time at the University of Cincinnati does not exclude the personnel from outside consultation contact. The duties and functions of these several groups are coordinated in the care of patients, in teaching, and in research.

While, as previously stated, the Professor of Pediatrics is medical director of the several organizations and institutions affiliated with the department, some of them have assistant medical directors who are members of the full-time staff. Thus there is an assistant director of pediatrics and of contagious diseases in the Cincinnati General Hospital, an assistant medical director of the Babies' Milk Fund Association, and also one of the Convalescent Home. All members of the medical staff of the affiliated institutions are nominated to the respective boards by the Board of Trustees of the University of Cincinnati, so that they become members of the Pediatric Department and under its supervision.

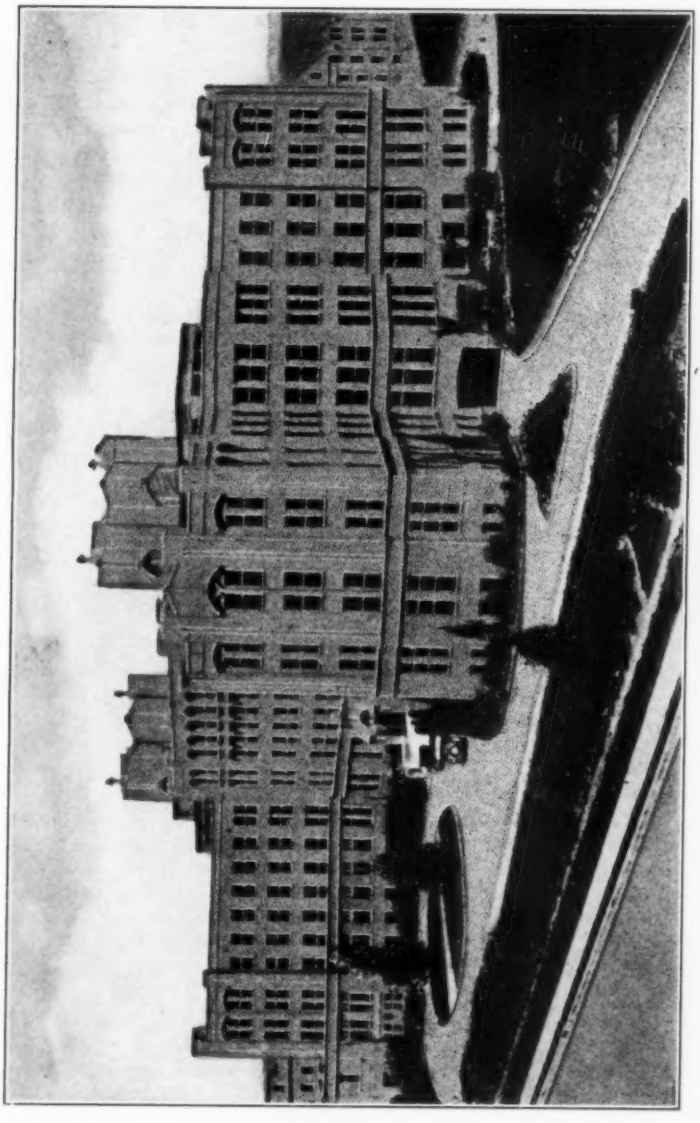
The pediatric resident staff works as a unit in the institutions previously mentioned; the group consists of three chief residents, one in the Children's Hospital, one in the Pediatric Division of the General Hospital and one in the Contagious Disease Hospital. There are ten assistant residents. In addition to these thirteen residents, there are six internes secured by rotation from the Cincinnati General Hospital and Christ Hospital, thus making a total house staff of nineteen. The chief residents have been at least three years out of medical school, and the assistant residents must have, as a minimum for acceptance, a year in a rotating interneship.

In the Research Foundation there are in addition to the director and director of laboratories, five fellows, two research scholars, and twenty-one research assistants and other personnel members such as librarian, photographer, mechanics, animal caretakers, etc., making a total of thirty.

OPERATION

In previous publications in which the work of the Pediatric Department has been described,[1, 2, 3, 4, 5, 6] it has been maintained that its activities should be directed into several different channels, all of which are closely related and complementary to each other. These are the care of patients, undergraduate teaching, graduate teaching, investigation, and public health activities.

Care of Patients.—All infants and children in the three hospital units are under the supervision of the pediatric staff, with physicians specially trained in the several specialities acting as consultants. That is to say, all children are patients of the pediatricians with surgeons, orthopedists, otolaryngologists and the like acting as consultants. No child can be admitted either to the in-patient or out-patient department of these institutions except from the pediatric service, and no patient can go directly to any special clinic, such as surgical or dental, without being referred there by the pediatrician. After discharge from the hospitals, the children are referred to their own physicians if they have sent them in to the hospital, or are returned to the proper out-patient clinic. The clinic of the Children's Hospital is operated on an appointment basis. The out-patient clinics are staffed by the resident physicians and by members



The Children's Hospital

of the full-time, part-time and voluntary visiting staff. The Social Service Department, especially in the Children's Hospital, is well organized, and there is follow-up service of these patients in their homes.

Many children recovering from acute illnesses or suffering from chronic noninfectious diseases are referred to the Convalescent Home.

Undergraduate instruction of medical students is given in their third and fourth year in the College of Medicine. Each student receives a total of about 300 hours in pediatric and contagious disease, during which he is under supervision by members of the teaching staff. In addition he has an hour and a half each day during the pediatric semisemester for study of patients or work in the library.

In the junior year there are courses on normal growth and development and nutrition, and sixteen hours are also devoted to lectures and clinical demonstrations of the acute infectious diseases.

In the senior year each student spends one-half a semester in pediatrics, this time being devoted to work on the wards, in the Out-Patient Clinic and in classroom demonstration and discussion. Each student receives an introduction to the types and methods of public health pediatric work and to the essentials of preventive pediatrics. Work in the Contagious Wards is also carried out during this semisemester. The students work in the Pediatric and Contagious divisions of the Cincinnati General Hospital, in the Children's Hospital, in the Babies' Milk Fund Association clinics, and in the Convalescent Home. Throughout the senior year there is a weekly clinic in which, by didactic and clinical demonstration, important subjects are discussed.

There has been organized an Undergraduate Pediatric Club in which students present the results of their own investigations, review current pediatric subjects, and discuss others that arise in the course of their undergraduate class work.

Graduate instruction is, in general, informal in nature, each graduate student acting as a resident in one of the institutions controlled medically by the Pediatric Department. These residents serve on a rotating clinical service in the pediatric wards, the Contagious Hospital, the out-patient clinics, the Convalescent Home, the Tuberculosis Preventorium and in the Child Welfare clinics. They are always under close supervision of staff physicians. Emphasis is placed upon following the entire course of the child's illness and his convalescence, and later upon maintaining him, if possible, in a state of health.

The second phase of graduate instruction is that of clinical research and the study of pediatric literature. The graduate students and residents are kept informed of problems of investigation being carried out in the wards, in the clinics and in the laboratories, and under certain suitable circumstances they may participate in them. Reports are made in biweekly meetings in which the clinical and research departments meet with the resident groups. These graduate students may receive university credit, and, after two years, a master's degree, provided that they pass the proper examinations and submit a suitable thesis.

The resident group has its own weekly meeting supervised by a member of the staff in which there is discussed the clinical material, and in which particular consideration is given to the patients who have been discharged during the week or who have died. So-called grand rounds are made weekly. The pathologist of the hospital holds frequent meetings to discuss the gross and microscopic findings in cases which have come to necropsy.

Research in the department has subdivisions into clinical investigation and departments of chemistry, bacteriology and metabolism. It has been recognized that these are not separate departments but that the subdivisions are working together

primarily in the solving of clinical problems. The primary aim of the Research Division of the Pediatric Department is to coordinate clinical and laboratory research.

Public health work in pediatrics in Cincinnati is so organized that a very large part of the supervision of the health of preschool children of the indigent group is directed by the Pediatric Department and so that the department can offer the close cooperation and assistance of its staff, clinics, and hospitals for the medical care of school and institutional children.

Members of the Pediatric Department serve on various committees and councils, such as the Medical Milk Commission, the Child Hygiene Council, the Public Health Federation, and other groups interested in the care of children. The effort is thus made to have the Pediatric Department function throughout the community even in those organizations for the work of which it is not entirely responsible. In the care of patients as well as in teaching special stress has been placed upon the correction of physical defects, immunization, prenatal care, the teaching of health habits, proper dental care, and, in general, all of the subjects which might be included under the general term of preventive pediatrics.

In addition to those functions mentioned, the Pediatric Department lends its assistance in the instruction of undergraduate and graduate nurses and gives courses in pediatrics for students in the Departments of Dietetics, Social Service, Child Care and Training.

Chart 1 gives an outline of the functions of the Pediatric Department.

PEDIATRIC DEPARTMENT, COLLEGE OF MEDICINE, UNIVERSITY OF CINCINNATI

TEACHING	CARE OF PATIENTS			INVESTIGATION (CLINICAL AND LABORATORY)
	OUT-PATIENTS	IN-PATIENTS	OTHERS	
Undergraduate students	Children's Hospital	Children's Hospital	Day nurseries	The Children's Hospital Research Foundation
Graduate students (including resident physicians)	Cincinnati General Hospital	Cincinnati General Hospital	Special schools (Board of Education)	Children's Hospital
Post-graduate courses	Contagious Disease Hospital	Convalescent Home Preventorium	Mothers' Training Center (Nursery school)	Cincinnati General Hospital
Nurses	Welfare Stations	Tuberculosis Sanatorium		
Social workers				
Dietitians			Summer camps	Welfare stations
Teachers				Day nurseries
Mothers				
Seminars				Schools
History meetings				
Pediatric Club				
Full-time, part-time and voluntary personnel				

Chart 1.

Chart 2 gives an outline of certain aspects of student instruction.

STUDENT INSTRUCTION	
1. UNDERGRADUATE	2. GRADUATE
a. Third Year— Infant Feeding Growth and Development Contagious Diseases	1. Rotating ward service: Medical Surgical Orthopedic
b. Fourth Year—One-half of one semester Diseases of Children Lectures, demonstrations Ward and Out-patient Dispensary Instruction Preventive Pediatrics Contagious Diseases	2. Out-patient Dispensaries 3. Convalescent Home 4. Tuberculosis Sanatorium and Preventorium 5. Infant Welfare—preventive pediatrics 6. Research 7. Weekly clinical demonstrations 8. Weekly reports of investigation 9. Pediatric Seminar (monthly)
c. Undergraduate Pediatric Society	
3. NURSING	4. OTHER DEPARTMENTS
Undergraduate { Lectures and ward Graduate { demonstrations	Dietetics Social Service School of Child Care and Training, of the University of Cincinnati

Chart 2.

REFERENCES

1. Mitchell, A. G., and Greenebaum, J. V.: Med. Bull. Univ. Cincinnati **5**: January, 1928.
2. Dreyfoos, Max: J. Med. Cincinnati **10**: 228, 1929.
3. Lyon, Robert A.: J. Med. Cincinnati **10**: 233, 1929.
4. Mitchell, A. G.: The Department of Pediatrics, College of Medicine, University of Cincinnati—Methods and Problems of Medical Education, Eleventh Series, The Rockefeller Foundation, New York, 1928.
5. Mitchell, A. G., and Bachmeyer, A. C.: Mod. Hosp. **34**: 56, 1930.
6. Mitchell, A. G.: Arch. Pediat. **49**: 181, 1932.

CHILDREN'S HOSPITAL, ELLAND AND BETHESDA AVENUES

Critical Review

NUTRITION OF THE NORMAL INFANT

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THIS review concerns itself with certain fundamental concepts pertaining to the nutrition of the normal infant. An attempt is made to compare current teaching and practice by the medical profession with experimental studies based on observations of the response of the human infant and of animals to various controlled nutritional regimes. In its preparation, three sources of material have been used freely. Two of these are recently established periodical reviews of published literature pertaining to fields allied to nutrition.[1, 2] The third is a questionnaire sent to more than a hundred outstanding pediatricians in this country. This consisted of thirty-five questions designed to obtain specific information concerning the views held and the practices followed in the field of normal nutrition. The detailed nature of the questionnaire makes the writer appreciate more deeply the extraordinarily generous response elicited from the physicians to whom it was sent. Apparent variation in interpretation of some of the questions makes it impossible to tabulate the answers statistically. It has been possible, however, to determine the majority opinion concerning most of the phases under consideration.

Present opinion continues to support the belief that human milk is the food of choice for the normal infant. The comment pertaining to infant nutrition in the section on growth and development in the White House Conference report[3] seems to express the views of the majority as elicited by the questionnaire. This states that breast milk must be considered better than the best of artificial foods for the first few months of life. It stresses the greater digestibility, the homologous nature of its proteins, its freshness and freedom from bacterial contamination, and avoidance of socio-economic and bacterial difficulties and hazards encountered with infant feeding. A minority opinion of significant numbers expresses doubt or disbelief that the advantages of human milk are still manifest when it is necessary to give the milk from a bottle. From the standpoint of convenience and socio-economic advantage, measures for the maintenance of adequate lactation and continuance of breast feeding, at least throughout the first months of life, are conceded quite universally to be desirable.

It has been assumed that the milk of a species is intrinsically superior to any modification for the nutrition of its young.[4] This concept of human milk as a "vital" fluid has played a large part in the formation of conclusions concerning infant feeding. The rate of growth of the average breast-fed infant is generally conceded to be that most desirable, and deviations from this standard are subjected to scrutiny. Before

In the compilation of data, the writer wishes to acknowledge assistance received from the American Dietetic Association through the work of Miss Margaret Ohlson.

acceptance of such a postulate, it should be established that human milk is quite constant in its composition, independent of the food of the mother, and that its composition offers the various essentials of nutrition in amounts sufficiently large and of such proportions that an adequate margin of safety exists. For extracted human milk to maintain outstanding advantages, it should be demonstrated to be safely free from bacterial contamination and from changes in its composition after extraction; moreover, its superiority to other types of milk should be made apparent. A distinction should be made between conclusions derived from precedent and uncontrolled clinical observation and those based on carefully controlled scientific studies. In reviewing published reports in the field of nutrition, it is often difficult to evaluate accurately the data presented. When the degree of control of experimental conditions is not similar, it is not possible to compare fairly one study with another. The value of some of the earlier data is lessened because of the nonrecognition of the importance of such control. Very probably future investigations will indicate fallacies in some of the work which at present seems quite conclusive. Any current review must be interpreted only as an index of opinion as determined from the material available at the time.

Recent investigations indicate that milk secreted by different women may vary widely in composition. It will be affected by the size and structure of the breast; by the amount and kind of food intake; by heredity, environment, and emotion. The quantity and quality of the milk vary in the same person.[5] Herz[6] noted that the calcium content of milk from wet-nurses varied from 8 to 15 per cent when the output under high calcium diets was compared with that under low calcium intake; the addition of calcium in the form of malonate or citrate caused no significant increase in the lowered calcium content of the milk. Wardlaw and Dart[7] found positive correlation between the weight of breast-fed infants and the weight of the various constituents found by analysis in the milk they received. Telfer[8] found that the milk from mothers from the industrial class was poorer in some of its constituents than the average values, and noted some differences between the composition of milk from rural as compared with urban mothers. In some instances the values found were so low that the adequacy of the milk for infant feeding was open to question. He found that the milk of the goat offered no adequate margin of safety when used by its own young; a slight diminution in its normal mineral content led to the development of osteoporosis and stunted growth; addition of a slight excess led to evidences of perfect health and to denser bone. He concluded that the mineral content of milk cannot be reduced, even in slight degree, without harmful consequences, either in the goat or in the human. Too long continuance of breast feeding entails grave risk of mineral insufficiency. The possibility of qualitative inadequacy of human milk is of increased significance when considering the food supply of the premature babe, or of the full-term infant born with reduced stores of minerals or other growth essentials.[9]

To make human milk available for a larger group of infants, human milk depots have been established and procedures developed to safeguard the quality of the product.[10, 11] Münchberg and Warkany[12] have made bacteriological studies of human milk offered in this manner and concluded that it is very difficult to preserve human milk which has been collected by a pump. Even when collected in sterile containers

and suitably refrigerated, bacterial growth was observed, together with dependent chemical alteration in the milk.

If formulas of such a nature that nutritional and digestive requirements are fully met can be prepared easily and cheaply, the need for the merchandising of human milk is minimized. Many reported studies give the impression that artificial feeding can meet these requirements. Durand[13] has called attention to the steady decline of infant mortality in the artificially fed group and states that results of artificial infant feeding under most skillful direction closely approximate, perhaps equal, those of successful breast feeding. Dennett and Craig[14] report observations of over 400 infants fed successfully on four different kinds of foods, including human milk; they imply that they encountered more disturbances of digestion in the group receiving human milk than among any of the others. Many other references could be cited to indicate that with suitable precautions appropriate types of artificial feeding do not increase the likelihood of infant mortality above that of the breast-fed infant. Growth statistics for both artificially fed and breast-fed infants indicate that the growth rate is dependent on the amount of food intake; the rate of the former group, when suitable formulas are administered adequately, equals or surpasses that of the latter group.[7, 15, 16, 17]

Conclusions based solely upon anthropometric studies do not appeal to the critical physician, who is accustomed to evaluate the health of the infant on the basis of the turgor of the tissues, the color of the skin and mucous membranes, the degree of physical achievement, and other criteria of a less tangible nature. Before the adequacy of any system of nutrition, either natural or artificial, can be considered established, some finer method of appraisal should be employed. Efforts to supply such information have led to chemical studies of the adequacy of growth. Through such studies, comparison is possible between the intake and excretion of various substances essential for normal growth and nutrition. The differences between the intake and the excretion represent the retentions of the substances in question. When such studies are performed properly and interpreted correctly, they offer data of incomparable value in determining adequacy of nutritional process. Metabolic data of this type are now available in amounts sufficient to serve as a basis for conclusions concerning the utilization and relative value of various types of infant foods. Because of lack of standardization of technic, it is not possible to compare all data on a quantitative basis. Isolated studies cannot be used as evidence for far-reaching conclusions. Nevertheless, general conclusions may be drawn justifiably from the assembled published data. Only representative studies published during the past decade need be presented here.

The procedure employed in such studies consists essentially in maintaining the subject on a diet of known and quantitatively constant chemical composition for a preliminary period of several days, this to be followed by a period of continued identical diet control during which all urine and feces are collected quantitatively. The excretions, together with an aliquot amount of the diet, are analyzed separately for their content of the factors being studied. Those customarily given chief consideration in this connection are calcium, phosphorus and nitrogen. Regardless of the level of intake of these substances, excretion of varying degree is always observed. Hamilton[18] has expressed the usually accepted concept, that such excretion represents the amount of

each substance needed for body maintenance, whereas that retained is used for growth. In commenting upon the requisites of a valid metabolic balance study in infancy, he postulated that repeated collections for a period of at least a month are necessary to establish qualitative or quantitative data concerning retentions.

Numerous workers, employing balance studies with acceptable technic, have established beyond question that the relative utilization of calcium and of phosphorus by the infant is more complete when human milk is used than when the child receives milk from other sources.[8, 19, 23] The significance of this fact is minimized when it is noted that the same workers found that the actual amounts of these minerals retained was higher with cow's milk than with breast milk, even though the utilization appeared to be less efficient. If it were necessary to assume that human milk is superior to any substitute as a food for the infant, then the higher retentions of minerals when cow's milk is fed would be interpreted as undesirable and possibly deleterious. Rominger and Meyer[22] speak of the increased retention resulting in a "supermineralization"; they did not notice any period of outwashing of the retained mineral over an observation period of three months, nor any evidence that harm resulted from retention. For this reason, they considered such retention to be physiologic. Boldt, Brahm and Andresen[23] observed infants receiving diluted cow's milk for a month, preceded and followed by similar studies when breast milk was fed. They found highest retentions with cow's milk, but also noted that the retentions with the second period of breast feeding were lower than in the first period. They interpreted this as evidence that the excess storage of mineral during the cow's milk period was washed out during the subsequent breast-milk period. Telfer[8] felt that the increased content of mineral in cow's milk was not needed, and that it placed an unnecessary load on the eliminative organs. In general, these views were those commonly accepted up to the past decade.[4] Interpretations quite different have been made during recent years. Analysis of cumulative data of many workers establishes that the retentions of calcium, phosphorus, and nitrogen are roughly proportional to the intake, and are determined largely by the amounts ingested. Since the mineral content of human milk is considerably less than that of cow's milk, mineral retentions are comparably lower with human milk ingestion than with cow's milk, unless the latter is diluted to an unjustifiable degree. Shohl, Wakeman and Shorr[24] found that when an infant received skimmed milk in which the salt content had been doubled, the retentions were increased proportionately. They state that it is well recognized that the body will not store permanently any more of a single constituent than it needs for its normal development. They comment further that it becomes increasingly important to know whether salt metabolism is a limiting factor in growth, and whether it can be affected favorably by offering a more liberal supply of mineral elements in the food of infants. The reports of Daniels, Hutton, Stearns and Hejinian,[15] of Nelson[16] and of Jeans and Stearns[25] offer good evidence that growth and retention of minerals and of nitrogen are roughly proportional to the amounts of calcium, phosphorus, and protein and other essentials for normal nutrition included in the daily intake. The children in the three studies just named showed rates of growth well in advance of the averages for the community. No evidence of harmful effect of any kind was noted in these rapidly grow-

ing infants; on the contrary, they seemed extraordinarily superior in health and in physical achievement. The mineral retentions observed with human or with cow's milk feedings are augmented markedly when cod liver oil is given.[15, 19] If the bogey of "supermineralization" is to be feared, and if mineral retentions observed when human milk alone is fed are to be considered most desirable, it is inconsistent to give the breast-fed infant cod liver oil since this will increase his retentions of minerals.

The data presented seem to indicate that acceleration of growth, physical achievement, and increased retention of the substances used in growth, are to be expected when the diet offers increased amounts of such nutritional requirements. Just as greater retentions are noted with dilute cow's milk feeding than with breast milk, still greater retentions are found when undiluted milk is fed. Conversely, there is good evidence to indicate that inadequate food supply, either before or after birth of the infant, will lead to lessened growth and to poorer quality of tissues. Toverud's[9] study of the physique at birth of infants of underprivileged mothers indicates that such infants are smaller than the average for the community and that by suitable prenatal nutritional and obstetrical care this handicap can be avoided. The differences noted evidently were primarily dependent upon nutritional inadequacy. Apparently the factor of prematurity was given due weight in her compilations. Wardlaw and Dart[7] studied a large series of breast-fed children in Australia, and correlated the growth rate with analysis of the milk from one breast four hours after nursing. They found a definite correlation between the weights of infants at various ages and the volume of milk obtained, together with its content of various constituents. They concluded that the relatively heavier infants have available a more plentiful food supply than lighter infants. Sherman and Booher[26] have shown that the quantity of calcification of bone of the rat at a given age is parallel to the level of intake of minerals up to that time. Hogan[27] has shown similar differences between the degree of mineralization of bones of hogs receiving varying amounts of minerals in their diets. There is no reason to believe that the same is not true in the human being.

The question arises as to the desirability of increased degree of mineralization and of accelerated growth during infancy or other period in childhood. The effect upon the health of the adult and the duration of life might be adverse. McCay[28] has discussed these phases, and implies that rapid growth with early attainment of maturity is incompatible with longevity and that the best chance for a long life span seems to favor the animal that has grown slowly and matures late. His beliefs seemed to be substantiated by his observations of the growth of trout. His conclusions are utterly different from those reported by Sherman.[29] Commenting on a study of longevity of rats as affected by diet, the latter states, "We have families of rats which are thriving in the twenty-seventh generation on a uniform diet—certainly a sufficiently rigorous demonstration that the diet is entirely adequate. Yet on enriching this already adequate diet in certain of its chemical factors by increasing the proportion of milk in the food mixture, there results an improvement in the general nutritional condition as shown by a whole series of criteria, such as more rapid and efficient growth, lower death rates and higher vitality at all ages, an increase of 10 per cent in the average longevity of adults, and greater extension of the prime

of life in that maturity is expedited and senility deferred in the same individual." Smith[30] in a review of some biochemical aspects of growth, states that increase in stature and change in body form of human beings have been observed under more favorable conditions of hygiene and of nutrition. Osborne and Mendel[31] had noticed rising standards of growth in experimental colonies of rats over a period of years; in 1926, commenting on this, the observation was made that whether the accelerated growth represents truly "normal" growth remained to be ascertained. Recently reports have been published of a study designed to answer this question. Outhouse and Mendel[32] observed rats maintained under similar conditions except for rate of growth; this was regulated through manipulation of the diet. In one study, growth was stimulated by adding graded amounts of "growth promoters" (lettuce and yeast) to a synthetic diet; in another study, the intake of protein, mineral, lettuce, and yeast was kept constant, the rate of growth being controlled through variation of the caloric intake. They found that, although it was possible to accelerate growth markedly by either method, there was no good evidence that in the rat such rapid growth led to an adult physique of larger proportions than those observed in the more slowly growing animals. In this connection they quote Merrill's[33] conclusion that there is no evidence that the human adult weight is associated with the initial rate of growth or that a larger size can be achieved through a rapid inherent growth than through a slower rate of growth. Some interesting variations were noted by Outhouse and Mendel in the composition of the bones of rats in the various groups. When bones of animals of the same size were compared, they were found to weigh essentially the same regardless of the rate of growth, chronological age or method of feeding that had been employed. However, the rapidly growing rats receiving lettuce and yeast supplements had bones with lower mineral content than was noted in the other animals, even though their rate of deposition of minerals was faster than that of their slow growing controls. No such differences in degree of mineralization was noted in the rats of varying growth rates which received equal amounts of minerals in their diets. These observations may offer an analogue to the bone changes noted by x-ray in children growing rapidly on diets of high mineral content. Roentgenologically these have been termed indicative of rickets, yet retentions of minerals, serum chemical studies, and clinical course indicate that no rickets is present. Infants on less adequate diets, growing at equal rates, might show true rickets.[16, 34, 35]

Summarizing the available information concerning rapid growth of infants receiving diets high in minerals, there is available no evidence to indicate that such rapid growth is deleterious, if the diet is adequate throughout. With such diets, the tissues are well supplied with all the materials used in growth. There is nothing to indicate that such rapid growth will lead to excessive stature in the adult. In fact, clinicians using feedings of this type have remarked that after a period of such rapid growth, the rate may become checked in late infancy and seem stationary for an indeterminate period before the usual rate is resumed.

In designing a formula for the artificially fed infant, what should be the goal? Macy has stated that it should be to surpass breast milk, not to equal it. The philosophy that the composition of breast milk offers the best proportions for the artificial formula has given rise to

the promulgation of numerous proprietary foods designed to provide a product of chemical composition similar to human milk. It often escapes the attention of the physician that even though the proximate analysis of such food may resemble closely that of human milk, the nature of its ingredients may be very different. The characteristics of milk proteins afford an excellent example. Human milk with a protein content of 1.5 per cent seems to meet the needs of the infant. It does not follow that any milk modification providing equivalent amounts of protein would be equally adequate, unless the protein were chemically, and possibly biologically, identical. Lactalbumin, which comprises 60 per cent of the protein of human milk, is better adapted for the maintenance of nitrogen equilibrium in man than is casein.[36] Cow's milk, although it has over twice the protein content of human milk, has a much lower proportion of lactalbumin; consequently, higher total protein allowance is necessary to assure nitrogen retentions of equal value. Because of such intrinsic differences between human milk and its substitutes, the composition of human milk does not offer an optimum pattern for the artificial formula.

Nitrogen retentions of satisfactory degree are observed when cow's milk allowances equal to 1½ to 2 ounces per pound per day are fed. When other proteins are used wholly or in part in the formula, the possibility that their nature may impair their adequacy must be kept in mind. Recent studies reemphasize the nonutility of gelatin as a source of body-building protein.[37] Evidence of inadequacy of the protein of the soy bean as a complete protein has been offered.[38]

The prime purpose in modifying cow's milk for the infant is to render the protein more digestible. This can be done through dilution, using water with or without added ingredients for the purpose. Another method quite widely used is that of acidification, either partial or complete, using lactic, citric, acetic, or any other suitable organic acid for the purpose. The use of evaporated or dried milk for infant feeding owes much of its success to the fact that during the processing the nature of the protein is changed so that such curd as is precipitated in the stomach remains flocculent and soft. Various types of milk modification have proved successful in the hands of physicians accustomed to their use. One prominent pediatrician has stated that probably four-fifths of normal infants could digest whole cow's milk without modification from birth, but that feeding procedures are directed toward the remainder.

Many clinical reports are available to attest the utility of different forms of milk modification. Metabolic studies have been reported indicating the utility of sweet milk dilutions,[15] whole undiluted acidified fresh milk,[16] and acidified evaporated milk of similar concentration.[25, 39] It has been demonstrated that when evaporated (unsweetened) milk is diluted with an equal volume of water, it can be considered the equivalent of whole cow's milk and used safely as such in infant feeding. Marriott and Schoenthal[17] have discussed the clinical aspects of the uses of soured evaporated milk feedings, reporting comparative studies of 752 infants on such formulas as compared with 670 infants fed at the breast or with sweet milk formulas. Almost 600 of the former group were newborn infants. The formula employed consisted roughly of equal amounts of evaporated milk and the diluent, the latter containing lactic acid and corn syrup in appropriate amounts. Gauging the success of feeding on the basis of weight gain, they found that the evaporated milk group regained their birth weight the sooner, while in the older

group the average weight gain was the same on the two types of feeding. Achievement progress was similarly comparable. All infants appeared to digest the evaporated feedings well; during the summer months, fermentative diarrhea did not develop. In eleven premature infants receiving evaporated milk feedings, the food proved satisfactory.

Brenneman[40] has questioned the need for acidification of evaporated milk formulas. It was his belief that in the use of acidified fresh milk, the addition of acid was valuable primarily because of its effect in producing a flocculent curd, and that the reduction in the buffer value of the milk was not of great importance. When using evaporated milk, in which the processing had insured a soft curd, he felt the addition of acid was unnecessary. He studied the response of infants with infections to evaporated milk formulas with and without added lactic acid; over sixty infants were included in each group. No difference in response was noted between those receiving the acidified and the non-acidified formulas. Both groups showed satisfying gain in weight, and the feces resembled those observed with infants receiving human milk.

Hess, Chamberlain, and Robins[41] have studied the clinical use of commercially prepared liquid and dried lactic acid milk, comparing the results of their long-continued use with that of breast milk and of mixed feeding. Sixty-three of their 85 subjects received such preparations as the sole source or as a part of their milk supply, whereas 18 received breast milk without supplement. The periods of observation varied from four to ten months. The authors concluded that such products can be used clinically under the same conditions as cultured sweet milk or milk to which lactic acid has been added.

In summary, published reports indicate that suitable formulas prepared from sweet milk dilutions, acidified whole milk, evaporated or dried milk, with or without the addition of acid, can be used with every clinical evidence of success in the feeding of the normal infant. Metabolic studies have indicated that when suitably administered and supplemented with the other essentials of normal nutrition, each type of formula mentioned offers evidence of adequacy equal to that of human milk.

From about seventy answers to the questionnaire already mentioned the composite majority opinion pertaining to the prescription of formulas may be summarized as follows: The daily milk allowance is prescribed roughly on the basis of the weight of the infant although this is not used rigidly. The usual daily allowance is 1½ to 2 ounces of cow's milk per pound. There is no harm in permitting the infant to take as much of a well-designed formula at each feeding as it will take willingly. In designing the formula, no attempt should be made to simulate the chemical composition of human milk. Cow's milk is used routinely, practically without exception; about 10 per cent use goat's milk under special circumstances. The great majority make use of sweet milk dilutions; a smaller number employ acidified feedings routinely or for special purposes. Evaporated and dried milks are used by most, condensed milk by few. Much variation exists in the type of sugar employed routinely in infants' formulas; corn syrup and maltose-dextrin preparations of similar chemical composition seem to be preferred by most, although about half use sucrose routinely or occasionally. Many failed to comment as to whether the usually accepted standards for rate of weight-gain for the young infant represent the optimum rate for the normal baby. Over half of those replying state

that they feel that such standards are not optimum, and even more state that they should not be used as determining factors in calculating the infant's food requirements. Possibly it is correct to interpret the answers to indicate a majority opinion that more liberal allowances of food for the infant are desirable than the older teachings recommend. The clinical success of such policies may indicate that in the hands of the present-day pediatrician, the infant tolerates safely larger allowances of food than was thought practicable in earlier pediatric practice.

The majority of answers indicated a belief that the present-day practice of infant feeding by the general practitioner is inadequate. As suggestions for the alleviation of this condition, the trend of most answers was that educational programs should be worked out, directed toward the medical student, the interne, and the practitioner. Many indicated the need to carry the educational program to the parents. The need for simplifying the teaching of infant feeding was emphasized by many. Other answers emphasized the following: the placing of stress upon attention to the child as a whole; the differentiation of nutritional problems in the well and the sick infant, with chief emphasis on the former; lessened use of proprietary foods; less dependence for nutritional knowledge upon salesmen for proprietary foods; dissemination of knowledge of the basic principles of physiology of digestion and of metabolism. A majority of those answering favor the dissemination by the federal and state governments of acceptable formulas for infant feeding, but condemn similar activities on the part of lay organizations and food manufacturers.

The inadequacy of human or cow's milk as a sole source of food for the infant is well recognized. Supplementary foods of various types are added to the infant's diet soon after the termination of the neonatal period, in order of their need; although obvious evidence of deficiency disease does not necessarily appear if they are omitted, the latency and danger of such deficiencies are gaining general recognition. The infant born at term often is credited with a better store of growth essentials than he possesses.[9, 42] Although his reserves may carry him through the period of exclusive breast-bottle feeding and may be replenished upon the assumption of a general diet, it is considered good medical practice to prescribe the necessary food adjuncts before their need becomes manifest.

Certain of the essentials for normal nutrition are so ubiquitous in their occurrence that no care need be exercised to provide them in adequate amounts. Provisions should be made to insure sufficient amounts of certain minerals, especially calcium, phosphorus, iron, copper and iodine, the vitamins, proteins of types suited to the body's needs, and a total energy equivalent adequate for growth, repair, and activity. An evaluation has been made of the properties of the foods most frequently prescribed in the infant's diet, using data and statements from Sherman's *Chemistry of Food and Nutrition*.[43] The following paragraphs are based primarily upon this material, and in part consist of literal quotations from that text, even though such citation is not made. Pertinent references in the more recent literature are included as indicated.

Human milk, or cow's milk with added carbohydrate, if given in appropriate amounts, will supply most of the essentials enumerated above in sufficient quantity. While some of the constituents of milk are not present in large concentration, the volume of milk consumed

makes it an important source of many essentials. With this in view, it probably is the most important food source of vitamin G. Its content of vitamin B probably is adequate, even though the milk has been subjected to heat treatment. Milk heated in the fluid state for 6 hours at 100° C. lost only about a fourth of its vitamin B. The vitamin A content of whole milk, while not high, is constant, and whole milk can be considered an important source of this vitamin. The vitamin D content varies with the environment and the food of the cow; it is not great in amount, but is of significance in nutrition. The vitamin C content is definitely affected by heat-treatment, in varying degree. It is all destroyed in evaporated milk; boiling fresh milk in an open pan for five minutes caused the loss of one-fifth of its vitamin C content. The supplies of vitamins C and D in milk should not be considered adequate for the infant's needs. The iron content of human milk usually is higher than that of cow's milk, but this is not true in the case of underprivileged mothers; it may be no better than that of cow's milk.[5] In the latter, it is definitely not present in amounts adequate to meet all of the infant's needs and should be supplemented by some better source of iron.

Egg yolk offers a valuable supplementary food for the infant. Compared on the basis of solid matter, milk and eggs are equally good sources of vitamin B. Egg yolk also is a good source of vitamins A and G. Important amounts of vitamin D may be present, depending upon the environment and food of the hen. The greater acceptability of egg yolk over fish oil and the richness of the yolk in so many other nutritional factors as well as vitamin D, combine to make it potentially an important source of vitamin D in practice. The protein of egg is "complete" and of high biologic value. Although the percentage of mineral content of eggs is as great as that of milk, the small amounts of the former ingested as compared with the latter makes them quite negligible as a significant source of minerals other than iron. Egg yolk ranks among the highest of food sources of iron; moreover, there is little doubt regarding the assimilation and utilization of the iron compounds of eggs, since they serve for the production of all iron-containing tissues of the chick. The egg yolk also contains copper, probably in amounts sufficient for the body's needs.

Mackay[44] used ferric ammonium citrate as a source of iron in her outstanding study of the nutritional anemia of infancy and obtained excellent results. The dosage she employed was 4½ to 15 grains daily.

The published values of hemoglobin concentrations of supposedly normal infants from 2 months of age up to about 2½ years are considerably lower than accepted normals for older children and adults.[44, 47] Still lower values are found when inadequate intake of iron is provided. Elvehjem, Peterson, and Mendenhall[46] question whether these supposed normals for infants are optimal values, since they are about 20 per cent below the normal values for older children. These three state that the supposed normals for infants cannot be considered normal until one can assume that the infant in the average home is normal, and add that we have no proof for such an assumption. The study of hemoglobin values of infants receiving diets known to be effective in the formation of hemoglobin must be made to determine the possible response under such a regime.

The marked storage ability of the body for iodine is a great safeguard for the period of infancy. The iodine content of foods varies

widely, depending upon the locality where they are produced. It is noteworthy that cod liver oil is one of the richest food supply sources of iodine; the infant receiving cod liver oil regularly should suffer no iodine deficiency.

The infant's need for vitamins D and C is quite generally recognized. Vitamin D administration in some form often is instituted as early as the third week of life, and vitamin-C-containing foods, soon after. Cod liver oil is recognizedly suitable as a source of vitamin D, and in addition, it reinforces the supply of vitamin A and assures adequacy of iodine. The substitution of other potent fish oils for that of the cod probably is without objection, as long as the value of the product employed is well established. At present it is impossible to comment fairly in regard to the many concentrates of fish oils that have appeared on the market. After their worth has been determined, it may be found that their use is justified. Viosterol is not a concentrate of cod liver oil, nor does it contain any nutritional essential other than vitamin D. As a concentrated form of this vitamin, its use is recommended.

Cereals must be considered primarily as sources of energy. They may supply fair amounts of vitamin B. Cereal-protein is not particularly valuable for growth unless large amounts of it are fed. The iron content of cereal frequently is lost in a large measure through milling processes. The phosphorus present may not be in a form available for use, thus explaining the rickets-producing tendency observed by Mellanby when cereal is fed, and considered by her to be due to the presence of some deleterious substance termed "toxamine."[48] This property is lost upon acid hydrolysis, or is offset if the cereal is irradiated, or if vitamin D is administered with it. Although certain cereals may be used as a source of vitamin B when such reinforcement seems necessary sources such as brewer's yeast offer the vitamin in much more concentrated and dependable form. Cereal is not an essential in the diet of the infant, and may displace some article of food for which real need exists.

Vegetables and fruits serve to supplement in significant amounts the supplies of vitamins A, B, C, and G. Much variation is found in the proportions and amounts of each. The mineral content of vegetables may not be utilized,[49-51] and cannot be depended upon as a source of supply. They affect the emptying time of the intestine and bowel, the vegetables being retained longer than fruits.[52, 53] In all the studies, sieved spinach seemed betted tolerated and more completely utilized than other forms. Reiche[52] concluded that canned vegetables and fruits could be substituted safely for the fresh products when the latter were not available. Schlutz,[51] although recognizing the value of these foods in the infant's diet, concluded that they are negligible sources of minerals and that their favorable effect is due to other factors. He found that the iron of spinach was not retained; in fact, the output was greater than the intake in every instance.

The answer to the questionnaire concerning the use of supplementary foods in the infant's diet indicated that, although some divergence of opinion exists, the practice of the majority is quite uniform and consistent with the views expressed in the foregoing pages.

Cod liver oil is prescribed by practically all; the dosage varies but after its use has been established, the usual dose is a teaspoonful three times a day. Practically all prescribe its use before the end of the

first month; many commence its administration as early as the second week. Over half prescribe other fish oils as a source of vitamin D either routinely or for selected patients. About a third of the answers indicate disbelief of the need for concentrates of vitamin D for prophylactic purposes.

Orange and tomato juice are used practically without exception as sources of vitamin C; administration is recommended as early as the second week, and over half recommend that its use be instituted by the end of the first month. The usually prescribed amounts are from ½ ounce to 3 ounces or more per day, the larger amounts being prescribed for the older infants.

Although the majority employ cod liver oil, which is rich in vitamin A, only a minority state that they prescribe foods specifically because of their vitamin A content. Most answers express disbelief that concentrates of vitamin A are needed in normal infant feeding.

About a third stated that they prescribe substances as supplemental sources of iron, and believe that this is essential in feeding the normal infant. The substances designated for this purpose consisted chiefly of vegetables, egg yolk, and iron salts. Administration was recommended by the sixth month of life; by some, as early as the first month. Egg yolk is prescribed for the normal infant's diet by the majority of the whole group, starting its use by the sixth month; some prescribe it as early as the second month.

Sieved vegetables are added to the normal infant's diet by the sixth month by the majority; sieved fruits by about half of those who answered the questionnaire. Some prescribe these foods as early as the third month. Cereals are introduced into the diet at about the same age by the majority.

In view of the statement frequently heard that some infants cannot tolerate many of the foods mentioned, a question was included to determine the prevalence of such food intolerance. Ambiguity of the question makes it impossible to distinguish between reference to allergic and to gastrointestinal or digestive intolerance. However, the majority stated that in their contacts, food sensitivity was not encountered or was very rare. By those who have encountered much food intolerance, egg was mentioned as the most frequent offender, milk the second. A few mentioned intolerance to vegetables, fruits, or to cod liver oil.

Several answers indicated a belief that it is wise to diversify the infant's diet quite early in infancy, in order to offer general protection against dietary deficiency, and to accustom the infant to a variety of flavors and consistencies of food.

The answers concerning diet supervision of the older child will be considered in another review.

REFERENCES

1. Nutritional Abstracts and Reviews, Aberdeen University Press, Aberdeen.
2. Annual Review of Biochemistry, Stanford Univ. Publ., Series, M. Sc.
3. White House Conference, Section 1, Growth and Development, New York City, 1932, Century Company.
4. Lusk, Graham: The Science of Nutrition, ed. 3, Philadelphia, 1923, W. B. Saunders Company.
5. Macy, I. G.: Yale J. Biol. & Med. **4**: 451, 1932.
6. Herz, B.: Ztschr. f. Kinderh. **54**: 413, 1933.
7. Wardlaw, H. S. H., and Dart, E. E. P.: M. J. Australia **2**: 564, 1932.
8. Telfer, S. V.: Glasgow M. J. **113**: 246, 1930; also **114**: 10 and 265, 1930.
9. Toverud, K. U.: Am. J. Dis. Child. **46**: 954, 1933.

10. Chapin, H. D., and Royster, L. T.: Diseases of Infancy and Childhood, ed. 6, New York City, 1928, Wm. Wood & Co.
11. Blankenhorn, M. D.: Hygeia **11**: 411, 1933; Emerson, P. W.: J. PEDIAT. **2**: 472, 1933.
12. Münchberg, F., and Warkany, J.: Wien. klin. Wchnschr. **45**: 1209, 1932.
13. Durand, J. I.: J. A. M. A. **99**: 275, 1932.
14. Dennett, R. H., and Craig, J. D.: M. J. & Rec. **136**: 133, 1932.
15. Daniels, A. L.; Hutton, M. K.; Stearns, G.; and Hejinian, L.: Am. J. Dis. Child. **37**: 1177, 1929.
16. Nelson, M. V.: Am. J. Dis. Child. **39**: 701, 1930.
17. Marriott, W. M., and Schoenthal, L.: Arch. Pediat. **46**: 135, 1929.
18. Hamilton, B.: Boston M. & S. J. **191**: 339, 1924; also Hamilton, B., and Moriarty, M.: Am. J. Dis. Child. **37**: 1169, 1929.
19. Swanson, W. W.: Am. J. Dis. Child. **43**: 10, 1932.
20. Wang, C. C.; Witt, D. B.; and Felcher, A. R.: Am. J. Dis. Child. **27**: 352, 1927.
21. Witt, D. B.: Am. J. Dis. Child. **43**: 306, 1932.
22. Rominger, E., and Meyer, H.: Arch. f. Kinderh. **80**: 195, 1927; also München. med. Wchnschr. **80**: 879, 1933.
23. Boldt, F.; Brahm, C.; and Andresen, G.: Arch. f. Kinderh. **87**: 277, 1929.
24. Shohl, A. T.; Wakeman, A. M.; and Shorr, E. Y.: Am. J. Dis. Child. **35**: 576, 1928.
25. Jeans, P. C., and Stearns, G.: Am. J. Dis. Child. **46**: 69, 1933.
26. Sherman, H. C., and Booher, L. E.: J. Biol. Chem. **93**: 93, 1931.
27. Hogan, A. G.: Missouri Agric. Exp. Stat. Res. Bull. 167, 1932.
28. McCay, C. M.: Science **77**: 410, 1933.
29. Sherman, H. C.: J. A. M. A. **97**: 1425, 1931; also J. Nutrition **2**: 415, 1930.
30. Smith, A. H.: Yale J. Biol. & Med. **4**: 551, 1932.
31. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **69**: 661, 1926.
32. Outhouse, J., and Mendel, L. B.: J. Exper. Zool. **64**: 257, 1933.
33. Merrill, M.: Human Biol. **3**: 37, 1931.
34. Jeans, P. C.: Unpublished data (1929).
35. Mitchell, E. C., and Nelson, M. V.: J. A. M. A. **95**: 1896, 1930.
36. Lusk, G.: The Science of Nutrition, ed. 4, Philadelphia, 1928, W. B. Saunders Company.
37. Jones, D. B., and Nelson, E. M.: J. Biol. Chem. **91**: 705, 1931.
38. Shrewsburgy, C. L.; Vestal, C. M.; and Hauge, S. M.: J. Agric. Research **44**: 267, 1932; abstract from Ann. Rev. Bioch. 1933, (see ref. 2).
39. Niermann, M., and Winter, M.: Arch. f. Kinderh. **89**: 290, 1930.
40. Brenneman, J.: J. A. M. A. **92**: 364, 1929.
41. Hess, J. H.; Chamberlain, I. M.; and Robins, L. S.: J. A. M. A. **98**: 1250, 1932.
42. Strauss, M. B.: J. Clin. Investigation **12**: 345, 1933.
44. Mackay, H. M. M.: Med. Res. Counc. Spec. Report Series 157, 1931.
43. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 4, New York, 1932, The Macmillan Company.
45. Mackay, H. M. M.: Arch. Dis. Childhood **8**: 221, 1933.
46. Elvehjem, C. A.; Peterson, W. H.; and Mendenhall, D. R.: Am. J. Dis. Child. **46**: 105, 1933.
47. Merritt, K. K., and Davidson, L. T.: Am. J. Dis. Child. **46**: 990, 1933.
48. Mellanby, M.: Physiol. Rev. **8**: 560, 1928.
49. Bloom, M. A.: J. Biol. Chem. **89**: 221, 1930.
50. Edelstein, E.: Ztschr. f. Kinderh. **52**: 483, 1932.
51. Schlutz, F. W., and Morse, M.: Am. J. Dis. Child. **44**: 648, 1932.
52. Reiche, A.: Deutsche med. Wchnschr. **58**: 452, 929, 1932.
53. Langer, H.: Ztsch. f. Kinderh. **52**: 465, 1932.

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THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MONDAY AFTERNOON SESSION
JUNE 12, 1933

Round Table Conference on Intracranial Lesions in Newborn Infants

Leader: Dr. Ethel C. Dunham. Assistants: Dr. Warren R. Sisson and Dr. John C. Montgomery.

DR. DUNHAM, NEW HAVEN, CONN.—Numerous articles on the subject of intracranial lesions in newborn infants have appeared in the literature in recent years. There seems to be almost no aspect of this subject that has not been studied with the result that the mass of information has been bewildering.

My purpose in presenting this paper is to summarize the literature and thereby present to you points of view which may be useful in their practical application to the diagnosis and treatment of intracranial conditions in the newborn infant.

In considering the types of intracranial lesions that occur in newborn infants, those due to trauma during labor or at birth probably far outweigh all others in importance. These injuries consist of congestion, edema, concussion, fracture, and hemmorrhage. Congenital developmental defects of the brain occur probably next in frequency although their exact incidence is not known. Other lesions occur occasionally in the newborn infant, such as meningitis and tumors. Asphyxia, although ordinarily the result, may be occasionally the cause of intracranial lesions in that it may in itself bring about alterations in nerve tissue not at the present time appreciated. Convulsions, which may occur as symptoms of the conditions already mentioned, may also be evidence of tetany, and also possibly of toxic poisons transmitted from the mother through the placenta, or of chemical changes in the blood such as hypoglycemia and acidosis.

The discussion at this time will be confined to a consideration of the major and most frequent intracranial lesion, namely, hemorrhage, the others being referred to briefly in the discussion of differential diagnosis.

Intracranial Hemorrhage

It is difficult to arrive at any conclusions as to the exact rôle intracranial hemorrhage plays in causing death in the neonatal period. Figures based on pathologic reports vary within wide limits (from 2 to 90 per cent in 23 reports). These figures, of course, give merely the incidence of intracranial hemorrhage as found at autopsy. In many instances the presence of hemorrhage is recorded but no report given as to whether it was of sufficient size or so situated as to have caused death. Foote[1] has pointed out that hospital statistics show a higher incidence of birth injuries as a cause of death than is reported for communities as units. Thus,

in the District of Columbia, the deaths reported as due to birth injury were 6.7 per cent while in the Columbia Hospital the incidence was 9.4 per cent. Irving[2] reported the mortality in the Boston Lying-In Hospital from this cause as 0.7 per cent. In a study[3] of 939 births occurring in three hospitals of New Haven, intracranial hemorrhage was considered the cause of death in 0.6 per cent of infants dying in the neonatal period.

Studies of intracranial hemorrhage among infants who survive are less numerous than those among infants who die. They are also more difficult to evaluate because, as is well known, an exact clinical diagnosis is difficult to make, and because in many instances intracranial hemorrhage occurs but leaves no demonstrable residua. Sharpe and Maclaire[4] placed the incidence at 9 per cent; Roberts[5] at 14 per cent, the diagnosis being based on the finding of blood in the cerebrospinal fluid. In the New Haven study already referred to, the total morbidity from intracranial hemorrhage was 1.2 per cent, the diagnosis being based on clinical as well as laboratory findings.

Cause of Intracranial Hemorrhage.—Ehrenfest[6] has fully reviewed the literature on the mechanism of the causation of intracranial hemorrhages in newborn infants. He points out the older authors held that intracranial hemorrhage was chiefly meningeal and over the convex surface of the brain the result of the deforming and compressive effects of labor. The importance of tentorial tears resulting in rupture of tentorial vessels was pointed out by Beneke.[7] The mechanism involved in these lesions is thought to be molding, which increases the longitudinal diameter of the head and stretches the falx to the point of rupture of the tentorium. Schwartz[8] and also Rydberg[9] consider pressure changes of major importance. Schwartz' theory was that during labor a difference in pressure arises between the presenting part of the head after the membranes have ruptured (atmospheric) and the body (intrauterine pressure) which sends the blood from the body into the head or to the zone of lower pressure (suction effect), resulting in venous engorgement and stasis. Rydberg, on the other hand, explained the occurrence of hemorrhage on the basis of mechanical forces acting on the fetus during parturition, which tend to diminish the volume of the head and bring about anemia in the brain. The intracranial tension is raised by mechanical pressure resulting in congestion and rupture of vessels. He stresses the importance of the remittent brain pressure during labor, also local brain pressure accompanied by injury to brain substance giving rise to a general intracranial circulatory disturbance, as well as to bleeding. Limited vascular injuries may also give rise to bleeding as in tentorial tears.

There are a number of studies, notably those of Capper[10] and Yllpo,[11] which show that intracranial hemorrhage occurs more frequently in the premature than in the mature infant. The peculiar liability of the premature infant to intracranial hemorrhage is ascribed to the weakness of the vessel walls and to the softness and poor development of skull bones. It has been stated, on the other hand, that because of the small size of the head, the danger of trauma is lessened.

The exact relationship between idiopathic hemorrhage and birth trauma is difficult to determine. Warwick's[12] report of autopsies on infants with intracranial hemorrhage, in 38 per cent of which she found hemorrhage elsewhere (viscera or skin) focussed attention on the relation of spontaneous hemorrhage to intracranial trauma. The incidence found by her was not confirmed by Cruickshank.[13] Indeed, the exact incidence of hemorrhagic disease is not known. In the New Haven study, the incidence was low, about 0.3 per cent. Intracranial hemorrhage without other bleeding occurred in 1.2 per cent of the infants in the same series. Since studies of the bleeding and clotting time have not been made for a large series of cases of intracranial hemorrhage, the exact relation of hemorrhagic disease to intracranial hemorrhage is not clear.

Although pathologic studies are numerous, the exact rôle played by intracranial hemorrhage in causing death is not clear. The cranial contents are easily subjected to traumatization during the opening of the skull. The more immature the subject, the greater the difficulty in opening the skull and removing the brain without distortion of the picture. The value of histologic studies is weakened by lack of knowledge of the normal picture of the developing brain and by the inadequacy of older staining methods to show the structures involved.

Seitz[14] advocated immediate severing of the head and hardening by freezing before opening the skull. From his work we have a classical description of those hemorrhages which occur over the hemispheres. Beneke contributed a new method for opening the skull, the formation of a side window through which tentorial and subtentorial vascular lesions could be observed. Beneke's method, although the best for gross inspection of a vulnerable part of the brain, nevertheless, made gross inspection of other parts of the brain and histologic examination difficult. A modification of Beneke's method was Schwartz' contribution by which he demonstrated histologically the common occurrence of numerous small hemorrhages and areas of degeneration in the brain substances of newborn infants. Cruickshank has called attention to the fact that if autopsies are done soon after death, edema of the brain and meninges may be demonstrated, which may have been the cause of the death and which will be missed if the brain is hardened. Rydberg has described an autopsy technic requiring no fixation for gross examination. For histologic examination he uses, besides the usual methods, Hortega's special technic for staining glia and also Spielmeyer's for myelin sheaths. The more general use of these new staining methods will, no doubt, bring out many important changes in the brain of infants which have previously not been observed.

Clinical Diagnosis of Intracranial Hemorrhage.—A history of prolonged or precipitate labor, premature rupture of the membranes, difficult or instrumental delivery, abnormal presentation, and dystocia should indicate the possibility of the occurrence of intracranial injury to the infant. On the other hand, infants born when one or more of these conditions are present may be perfectly normal at birth and develop normally both mentally and physically. Moreover, infants whose mothers give a normal labor and delivery history may present symptoms of intracranial injury and show residua at a later time. The labor and delivery history, therefore, may or may not be significant. It is clear that a normal history never rules out intracranial injury, nor does an abnormal one presuppose it.

Many authors have stressed the variety of clinical manifestations of intracranial injury and the fact that none are pathognomonic. Appreciation of the widely variable pathology will make this obvious. Clinical signs of brain injury may be those of shock or increased intracranial tension caused by (1) general pressure on the engaged head during the second stage of labor, (2) edema, and (3) actual extravasion of blood into the meningeal spaces and ventricles or into the brain substance itself. If bleeding is definitely localized or, if clots form and organization takes place, localized signs of involvement of the central nervous system may be evident.

Considerable confusion, as to the earliest signs of intracranial injury, has arisen because observations have not been recorded at the time of birth and in the period immediately following. Such general symptoms as delayed onset of respirations, delayed or weak cry, pallor, cyanosis, twitchings, convulsions, hypo- or hypertonicity all point to the possibility of intracranial trauma. The fontanel may or may not be full, tense, or bulging. Unless the hemorrhage is a moderately large one (meningeal or ventricular) the fontanel will probably appear normal. The usual picture is that of some degree of shock. Paralyses of central origin will usually not be present at birth. The immediate interest of the physician in these cases is to

establish respirations, after which nothing further may be noted until difficulty in sucking and swallowing is encountered. If examination is made at this time, perhaps several hours after delivery, a different set of symptoms may be noted, such as respiratory irregularity, paralyses, nystagmus or strabismus. If hypotonic earlier, the infant may be hypertonic at this stage. Convulsions, which may occur first at this time, are usually general or involve first one side and then the other. A point to emphasize is the usual absence of localizing signs or of marked spasticity even several hours after birth. There are cases in which marked spasticity of extremities has been noted immediately after birth, but in our experience these infants have been found to be suffering from congenital cerebral defects. When seen at later times the neurologic picture has remained essentially unchanged, and microcephaly has become obvious, or postmortem examination has shown lack of cerebral development and absence of hemorrhage. This is the syndrome known as Little's disease, one which Ford[15] has pointed out to be usually of developmental origin. Permanent paralyses, unilateral or asymmetrical, resulting in spasticity and contractures, are usually late results of intracranial injury and, in our experience, have occurred a number of times in infants who had no evidence of involvement of the extremities early in life. Facial palsies may be seen immediately after birth and are more often peripheral than central in origin. Ocular palsies also may occur early and may persist as the only apparent late residua of intracranial hemorrhage.

The interpretation of eye signs such as nystagmus and strabismus is worthy of special comment. Fine oscillations of the eyes or even coarser nystagmoid movements are frequently seen in normal newborn infants. They probably represent the ineffectual beginnings of ocular fixation and are not to be considered pathologic. However, when nystagmus of wide range is associated with forced deviations of the eyes in any direction, particularly upward, intracranial damage is to be suspected.*

Movements of the eyeballs are not always conjugate, and rolling or wandering is frequently seen in the first days of life. It is difficult to distinguish the transient from the permanent type of strabismus at this time. What is thought to be a transient or mild squint in infancy may develop into a permanent squint at a later time.

Ophthalmoscopic Examination.—The common occurrence of retinal hemorrhages in the newborn is well recognized. The incidence, which is higher the more promptly after birth the examination is made, varied between 12 and 19 per cent, according to the reports of five observers. The hemorrhages may be considered evidence of congestion secondary to intracranial hypertension and not as indicating gross cerebral hemorrhage. Schleich's[16] theory is that the congestion is the result of compression of the cavernous sinus interfering with the normal emptying of the ophthalmic vein.

The testing of the superficial and deep reflexes gives, on the whole, little satisfactory information. This is due chiefly to two factors, the immaturity in anatomical development of certain structures (myelinization) and, as Putnam[17] has pointed out, to the lack of development, from the functional standpoint, of "the inhibitory and finer regulatory mechanisms of the 'higher centers,' particularly the cortex and pyramidal tracts, which later facilitate localized reactions." In other words, the response of the normal newborn infant to local stimulation is a general one, the total response being so marked that the local one is obscured. Examples are seen in the postural reflexes such as the Magnus phenomenon, or tonic neck reflex, and the Moro "start." These general reflexes, as well as local reflexes, such as the Chvostek, ankle clonus and Babinski, normally present in the newborn infant, usually have a pathologic significance only when associated with other abnormal

*This note on the eyes was dictated by Dr. J. C. Fox.

findings. The presence of the pupil reflex should always be determined. Rydberg regards "pupillar paralysis if complete and clearly unilateral" as "perhaps the most reliable indication as to the localization of the hemorrhages." The response to stimulation of the superficial and deep reflexes is so variable in the newborn infant that in the absence of other abnormal findings they are difficult to evaluate.

Laboratory Diagnosis.—The laboratory diagnosis of intracranial hemorrhage may be as difficult as the clinical diagnosis. When a lumbar tap is made, normal fluid may be obtained if the hemorrhage is intracerebral and, therefore, so situated that there is no communication with the intermeningeal spaces. When blood or blood-tinged fluid is obtained, the conclusion that there has been an intracranial hemorrhage is not, by any means, always justified. The membranes lining the canal and the vertebral discs are vascular; the canal itself and the space between discs small and easily traumatized by the needle. However, in the presence of a full fontanel, a lumbar tap which yields uniformly bloody fluid under increased pressure, is probably satisfactory evidence of intracranial hemorrhage, especially if the tension of the fontanel is relieved. To rule out infection, however, it is well to examine a drop of fluid for cells, to culture the fluid and to look for crenation of red blood cells. It is also important to centrifuge a bloody fluid so that the color and clarity of the supernatant fluid becomes visible. The presence of polymorphonuclear leucocytes or a high polymorphonuclear-lymphocyte ratio may be an important indication of infection which culture may confirm. A warning is in place here that when the history and physical examination make the diagnosis of intracranial hemorrhage probable and lumbar taps yield blood or bloody spinal fluid, a diagnosis of meningitis may be missed if the procedures outlined are not carried out. Early age does not rule out meningitis. Crenation of red blood cells in a drop of spinal fluid that is examined immediately after being taken indicates old hemorrhage.

The significance of a yellow tinge or xanthochromia of the fluid is not altogether clear and must be discussed somewhat in detail. The color may be due to pigment derived from bile or from broken down red blood cells. According to Glaser[18] and Levinson,[19] however, yellow fluids occur which give neither a positive benzidine nor Van den Bergh reaction. These authors consider the pigment an intermediate product between hemoglobin and bilirubin. Roberts[5] and Levinson and his co-workers[20] have pointed out the frequent presence of xanthochromia in normal newborn infants. In Robert's series of 423 cases, no fluid was obtained which was absolutely colorless. In Levinson's series of 100 cases only 12 had colorless spinal fluid. Sharpe and Maclaire[4] summarized the results of spinal punctures made within twenty-four to forty-eight hours after birth on 500 infants, recording as bloody or blood-tinged forty-five or 9 per cent. Yellow fluid was obtained in a number of these cases and was apparently considered evidence of hemorrhage. Glaser[18] reported the results of lumbar tap in 100 premature infants. In every spinal fluid taken from infants under sixty days of age, some degree of yellow pigmentation was found, and in a later report[21] of seventy additional cases the findings were confirmed. Glaser considers xanthochromia of the spinal fluid of premature infants physiologic; the icterus index paralleling that of the blood serum, an expression of anatomic and physiologic immaturity of the blood-cerebrospinal fluid barrier.

On the basis of these reports, the conclusion may be drawn that yellow spinal fluid is not necessarily evidence of intracranial hemorrhage, but may be only evidence of physiologic jaundice, even when jaundice of the skin cannot be seen. On the other hand, yellow spinal fluid found in the absence of jaundice and with the icterus index of the blood serum normal should be considered evidence of intracranial hemorrhage.

Spinal Fluid Pressure.—Sidbury[22] stated that the normal cerebrospinal fluid pressure in the newborn infant will probably lie between 2 and 6 mm. Hg. Levinson, Greengard and Lifvendahl[20] found that the pressure varied considerably according to the position of the needle; the type of needle and manometer used; the condition of the patient, whether quiet or crying; and the site of puncture. Lumbar fluid pressure varied between 1 and 6 mm. (av. 4.5); cisternal, between 4 and 40 mm. (av. 25). They considered a reading above 6 mm. Hg pathologic. Sharpe and Maclaire considered spinal fluid pressure readings above 5 mm. abnormal. Monroe[23] measured the cerebrospinal fluid pressure 142 times in ninety-five newborn infants (139 lumbar and 3 ventricular). He considers that normal pressure lies between 2 and 6 mm. Hg. Pressure below 2 mm. indicated the presence of surgical shock or dehydration. He found increased cerebrospinal fluid pressure in every case of depressed fracture, intracranial hemorrhage, cerebral edema, or cerebral congestion.

Differential Diagnosis.—Since the general symptoms of intracranial hemorrhage are not pathognomonic, some of their other causes should be discussed to aid in differential diagnosis. The most important is contusion or concussion, which can only be differentiated from hemorrhage in the more rapid recovery and lack of development of residua.

Asphyxia from prolonged labor, or cord and placental complications, may also give nearly the same symptom complex. Limits of time will not permit a detailed discussion of the rôle of asphyxia in bringing about hemorrhage or its possible rôle in causing damage to brain tissue in the absence of demonstrable hemorrhage. Experimentally, brain damage has been produced by asphyxia, and Zimmerman* has demonstrated similar lesions without evidences of hemorrhage in an asphyxiated infant who was considered clinically to have an intracranial hemorrhage. Narcotization of the infant from morphine given to the mother may also sometimes be difficult to differentiate from other cerebral conditions.

Treatment.—The treatment of infants with intracranial lesions cannot be determined by rule, each case being a law unto itself. Many methods of treatment have been advocated. General supportive treatment during shock followed by postural or operative procedures including in the latter drainage of meningeal spaces are the commonest.

It is the custom in many nurseries to lower the infant's head by raising the foot of the bassinet during the first day of life to permit free drainage of mucus or vomitus from the mouth. Riesenfeld[24] has suggested that the position should be reversed and that the infant should be raised to an almost vertical position when intracranial bleeding is suspected. In this position the venous pressure, as well as that of the cerebrospinal fluid is lessened.

Whether or not lumbar puncture should be performed is not clear although it is quite widely advocated in the literature both for diagnosis and treatment. There are several objections to withdrawing spinal fluid by lumbar puncture even when a few cubic centimeters only are taken for diagnosis. During this procedure the infant is subjected to handling, made to cry, and thereby intracranial tension is raised. Often no information can be gained because, if bloody fluid is obtained, trauma from the needle cannot be excluded. Removal of any amount of fluid may be a dangerous procedure, because as pressure is relieved, bleeding may be increased or the drawing off of even a small amount of fluid from below may cause herniation of the medulla. In the presence of a full, tense fontanel, if pressure must be relieved, it may be best to perform a ventricular puncture.

Repeated withdrawal of fluid has been advocated and relief of symptoms ascribed to it. Bagley's[25] work would seem to make recourse to immediate and frequent

*Personal communication.

withdrawal of bloody fluid imperative because he has shown that the mere presence of blood in the cerebrospinal spaces causes cerebral irritation and, if not removed, results in the development of a sterile meningitis with thickening of the meninges. A recent paper by Levinson and Saphir,[26] on the other hand, would lead to rather a different point of view, in that the meninges in the cases reported by them showed very little evidence of reaction even when gross bleeding into them was known to have occurred.

Cisternal punctures have been reported by Brady,[27] B. S. Dunham,[28] Levinson, Greengard and Lifvendahl,[20] and more recently by Kutscher.[29] The advantage of puncture in this region is that traumatic blood is almost never obtained, and therefore, the results of diagnostic punctures are much more dependable than when lumbar taps are made. Cisternal puncture, as well as spinal puncture, is probably contraindicated in the presence of a tense or bulging fontanel. A sufficient number of reports have appeared to make it apparent that cisternal puncture is probably a simple and safe procedure in the hands of those who are familiar with the technic. It probably should be resorted to when lumbar taps are dry, or appear to be contaminated by traumatic blood. It is not, however, entirely without danger since the needle may pierce the medulla if the puncture is not properly made.

Surgical treatment has been attempted, but it has met with little success. When, however, fracture of the skull is present, a surgical consultation should be sought.

From the point of view of prevention and treatment, the administration of whole blood intramuscularly or subcutaneously has been recommended. Reports claiming that the routine prophylactic administration of blood to every newborn infant in the delivery room has reduced the incidence of hemorrhagic disease and of intracranial hemorrhage are not very convincing since the incidence of these conditions before the institution of preventive measures has not been established.

Prognosis.—The prognosis as regards life depends on the size of the hemorrhage and its location. Hemorrhage below the tentorium is almost always fatal. Hemorrhages, by increasing intracranial pressure or by obstructing the flow of cerebrospinal fluid, cause interference with function of nerve tissue, and may result in death or in impairment of mental and physical health of survivors.

Those infants who survive may show immediate symptoms and signs of intracranial injury, which may persist or may disappear completely. It is conceivable that infants may suffer from intracranial trauma, the signs of which, not apparent at birth or during infancy, may appear in later life. Peterman,[30] for instance, in a study of the causes of convulsions, finds that cerebral birth injury, although the commonest cause in infants under one month, is second in importance as a cause of convulsions occurring from one to six months and third, from six to thirty-six months. The subject of the result of intracranial injury in surviving infants has not been very satisfactorily studied. The approach has been from two different angles. A number of studies have been based on statistical analyses of the birth histories of large groups of children mentally and physically handicapped. Dayton[31] found an association between a history of abnormal labor and neurologic defects and certain personality traits, but no association with low intelligence quotients. Schroeder,[32] on the other hand, found a relationship between mental retardation, behavior difficulties, and abnormal labor. The possibilities of error in the historical method are obvious.

The second method of approach is the follow-up of infants on whom a definite diagnosis of intracranial hemorrhage has been made at, or shortly after, birth to determine the late residua. About twenty reports, including a total of less than 300 infants, have been found, the age at time of reexamination varying between one month and eighteen years. Between 60 and 70 per cent of the infants are reported to show no residua. The condition at the final examination is usually

somewhat loosely described, and reports of mental tests are conspicuously lacking. The basis, moreover, for the diagnosis of intracranial hemorrhage varied in the different groups of cases reported. The finding of blood in the spinal fluid as the only criteria for a diagnosis of intracranial hemorrhage is not, we think, justifiable. Roberts,[5] on this basis, reported reexamination of fifty-four infants, only two of whom were found to be abnormal. Other authors, among them Monroe,[23] Fleming and Morton,[33] and Naujoks,[34] also report a low incidence of abnormal findings. The most recent report is that of Rydberg who found that of forty-eight infants with a clinical diagnosis of intracranial hemorrhage (exhibiting major cerebral symptoms during the first few days of life), nine were normal and ten showed an abnormal condition which did not handicap them or was not related to birth injury. Of the remaining twenty-nine infants sixteen were idiots or imbeciles; ten were backward children; one was epileptic; and two had serious conditions but were mentally normal.

In the New Haven study, twenty-seven infants were seen with major cerebral symptoms following birth. Twelve of these were considered to have intracranial hemorrhage, six of them dying in the neonatal period. Of the six who survived, when reexamined at one year: only two were found to have no residua; two showed spastic monoplegia; and two, ocular palsies.

The incidence of spastic diplegia (so-called Little's disease) was strikingly low, being found in only four of the two or three hundred cases of intracranial hemorrhage reported. This is in accord with Ford's[15] view that spastic diplegia with microcephaly is in the large majority of cases, the result of a congenital cerebral defect rather than an intracranial hemorrhage due to birth trauma.

In conclusion, it is hardly necessary to state that prevention of intracranial injury, although, of course purely an obstetric problem, is one with which the pediatrician should be familiar. The methods of prevention have been described in recent articles by Ehrenfest,[35] Adair,[36] Plass and Jeans.[37]

REFERENCES

1. Foote, J. A.: Diseases of the Newborn, Philadelphia, 1926, J. B. Lippincott Co.
2. Irving, F. C.: New England J. Med. **203**: 499, 1930.
3. Dunham, E. C.: Some Clinical Observations on 1,000 New-born Infants (in press), Tr. Am. Pediat. Soc., 1933.
4. Sharpe, W., and Maclaire, A. S.: J. A. M. A. **86**: 332, 1926.
5. Roberts, M. H.: J. A. M. A. **85**: 500, 1925.
6. Ehrenfest, H.: Birth Injuries of the Child, ed. 2, New York, 1931, D. Appleton & Co.
7. Beneke, cited by Ehrenfest.
8. Schwartz, cited by Ehrenfest.
9. Rydberg, Erik: Cerebral Injury in New-born Children Consequent on Birth Trauma; with an Inquiry into the Normal and Pathological Anatomy of the Neuroglia, Acta Path. et microbiol. Scandinav., Suppl. 10, 1932.
10. Capper, A.: Am. J. Dis. Child. **35**: 262, 1928; **35**: 443, 1928.
11. Ylipo, A.: Ztschr. f. Kinderh. **38**: 32, 1924.
12. Warwick, M.: Am. J. Dis. Child. **21**: 488, 1921.
13. Cruickshank, J. N.: Child Life Investigations. The Causes of Neonatal Death, Medical Research Council, Special Report Series, No. 145, 1930.
14. Seitz, cited by Ehrenfest.
15. Ford, F. R.: Medicine **5**: 121, 1926.
16. Schleich, cited by Ehrenfest, Birth Injuries of the Child, p. 91.
17. Putnam, M. C.: Preliminary Report of White House Conference on Child Health and Protection. Part I: 135, New York, 1930, Century Co.
18. Glaser, J.: Am. J. Dis. Child. **36**: 195, 1928.
19. Levinson, A.: Abt's Pediatrics, Vol. II, p. 120, Philadelphia, 1923, W. B. Saunders Co.
20. Levinson, A.: Greengard, J., and Lifvendahl, R.: Am. J. Dis. Child. **32**: 208, 1926.

21. Glaser, J.: Am. J. Dis. Child. 40: 741, 1930.
22. Sidbury, J. B.: Arch. Pediat. 37: 545, 1920.
23. Monroe, D.: J. A. M. A. 90: 1688, 1928.
24. Riesenfeld, E. A.: Arch. Pediat. 48: 728, 1931.
25. Bagley, C. V.: Arch. Surg. 17: 18, 1928.
26. Levinson, A., and Saphir, O.: Am. J. Dis. Child. 45: 973, 1933.
27. Brady, J. M.: J. A. M. A. 71: 347, 1918.
28. Dunham, B. S.: Am. J. Obst. & Gynec. 11: 833, 1926.
29. Kutscher, G. W., Jr.: Am. J. Dis. Child. 42: 1428, 1931.
30. Peterman, M. G.: J. A. M. A. 99: 546, 1932.
31. Dayton, Neil: New England J. Med. 203: 398, 1930.
32. Schroeder, P. L.: J. A. M. A. 92: 100, 1929.
33. Fleming, G. B., and Morton, E. D.: Arch. Dis. Child. 5: 361, 1930.
34. Naujoks, cited by Ehrenfest, Birth Injuries of the Child, p. 128.
35. Ehrenfest, H.: J. A. M. A. 92: 97, 1929.
36. Adair, F. L.: Mich. State M. Soc. J. 31: 363, 1932.
37. Plass, E. D., and Jeans, P. C.: J. Iowa M. Soc. 22: 443, 1932.

DISCUSSION

DR. JOHN C. MONTGOMERY (DETROIT, MICH.).—Dr. Dunham asked me to discuss the diagnosis and treatment from the standpoint of the practicing pediatrician. I was disinclined to consent because I had no fixed ideas and no strongly maintained convictions. On second thought, this is perhaps an asset and I may be able to stimulate more discussion by what I do not know than by what I claimed to know.

We have always felt that the diagnosis was dependent on the finding of definite neurologic changes; convulsions, irregularity in respirations, definite eye signs, with bulging fontanel and bloody spinal fluid, the release of which relieved the bulging of the fontanel. Even though the individual case may show these criteria, I believe we can seldom feel entirely sure of a diagnosis unless it is made either by autopsy or by time.

Looking at the problem of diagnosis from the standpoint of ordinary practice, I ask how frequently is intracranial hemorrhage diagnosed? In an effort to determine this, I wrote to all the hospitals in Detroit to ask what their incidence of cerebral hemorrhage and results were during the past five years. I did not have any reply which indicated both the number of cases and the number of deaths. The incidence varied between 0.28 per cent of cases of intracranial hemorrhage to 1.12 per cent of patients who died of intracranial hemorrhage. I may add that in one of these hospitals having the lowest percentage, I have personally seen a large number of cases of intracranial hemorrhage. The point to stress is that the average hospital has no figure of how frequently intracranial hemorrhage occurs. There is a great variation in the willingness of the staff to make such a diagnosis; there is a great variation, as Dr. Dunham pointed out, in the criteria for such a diagnosis. Obstetric skill varies a great deal and obstetric operative procedures change as well as anesthesia. Perhaps a function of the American Academy of Pediatrics might be to standardize the organization of data on the newborn and insist upon a certain amount of information being available. I know of no hospital in Detroit where the newborn are examined soon, or immediately after birth. Examination after birth and during the first few days of life might yield some very important information. During the past five or ten years, the largest proportion of intracranial hemorrhages we have seen have occurred in babies born in a relatively normal manner.

So many different treatments have been recommended that one is forced to the conclusion that no particular treatment is very efficacious. Various hemostatic procedures have been advised as well as drainage of the spinal fluid by spinal puncture and cisternal and ventricular puncture, or a combination of the two, and also many advise doing absolutely nothing. It is very difficult to determine just

how efficacious treatment is because these children are seen at birth and usually are not followed for a long period of time. The problem may be approached from either end by following them over the years, or when these children are seen at three, four and five years of age, by tracing back and finding out what the birth history was. It is very difficult. If we could have more accurate data from hospitals, it would be easier to arrive at some conclusion.

A consideration of the factors at work in the production of intracranial hemorrhage and the pathologico-physiologic processes, which nature sets to work once the hemorrhage has occurred, will make it clear why the picture is so complex. I have outlined in a chart the chief factors in the production of intracranial hemorrhage.

The first and most important is trauma. There has been a great deal of argument about the importance of a hemorrhagic tendency. I do not believe we can answer the question as to whether or not hemorrhagic diathesis is important in the production of intracranial hemorrhage. The important thing is that once hemorrhage has occurred, such a tendency is a factor in its maintenance. A baby with a large tear in its fontanel or with a ruptured superior longitudinal sinus will continue to bleed regardless of whether there is a hemorrhagic tendency or not, and a baby with a prolonged bleeding time will continue to bleed for a much longer time from a given injury than will one who has no such hemorrhagic tendency.

It has been shown that at the time of birth there is a sudden rise in the systemic blood pressure, which we can, for want of a better name, call neonatal hypertension. There probably are other factors which should be considered, such as capillary pressure and the fragility of the capillaries, particularly in the premature infant because it has been shown that the capillaries rupture more easily. I think this point may explain some of the cases occurring after birth by cesarean section because in these the factor of a sudden rise of blood pressure is present, and many infants so delivered are premature.

We have then these three factors: first, trauma; second, hemorrhagic tendency; and third, neonatal hypertension combining in the production of intracranial hemorrhage. As a result of the hemorrhage, we have first, an immediate fall in systemic blood pressure, and second, an increase in the intracranial pressure. These are factors tending to decrease the hemorrhage. However, because of these factors, there is frequently an inadequate circulation through the respiratory center with resulting asphyxia to combat which, there is a compensatory rise in the systemic blood pressure, which in turn has a tendency to enchance the intracranial hemorrhage.

It is apparent that the compensatory forces and processes set up in the body following intracranial hemorrhage are conflicting. We must realize that any therapeutic interference necessitates taking sides in this conflict. We should always pause and ask ourselves in all humility if we are justified in intruding. Present knowledge is not such as to guarantee that we are always on the right side when we interfere.

I have put on the chart the procedures we ordinarily employ. We give transfusions or employ other hemostatic procedures in order to control the hemorrhagic tendency. My own experience is that nothing will control the tendency to hemorrhage like an intravenous transfusion. I have felt that nothing was accomplished with intramuscular blood or other hemostatic procedures. However, a transfusion will temporarily, at least, increase the blood pressure. Decreased systemic blood pressure is one of the factors nature has interposed to control the hemorrhage. Even a transfusion may be extremely difficult to perform, and it may provoke a very considerable amount of crying and other exertion on the part of the infant during which time he is raising his own blood pressure and doing himself much harm.

Other therapeutic procedures commonly employed such as lumbar, cisternal, and ventricular punctures, are designed to relieve the increased intracranial pressure, which presumably is the direct cause of brain damage. Here again we are interfering with one of the compensatory factors which tend to control the hemorrhage. I have a growing conviction that such drainage should be resorted to either after we have given intravenous blood and have reason to believe the hemorrhage is under control, or to relieve severe convulsions.

Another point to be stressed is the position in which babies are frequently held when lumbar puncture is done. Acute flexion of the head unquestionably increases the intracranial venous pressure and increases the amount of hemorrhage. I have observed frequently the baby's symptoms becoming markedly exaggerated and the convulsions increasing during the time these procedures were carried out.

Experience has forced us to the conclusion that the milder cases of cerebral hemorrhage are best left strictly alone. We do not feel that we have accomplished anything by routine lumbar puncture or routine cisternal puncture. When convulsions are severe or extremely persistent and we feel it is necessary to drain the spinal fluid, contrary to the opinion of a great many others, we have frequently resorted to cisternal puncture. Although we always try the lumbar route first, when we are unable to get in, we make a cisternal puncture. Up to date we have had no ill effects.

Dr. Dunham's suggestion about ventricular puncture is an excellent one but not entirely devoid of danger, and the obstetricians will usually oppose it because they feel we are going to produce a hemorrhage if one is not already present.

There is another point to be kept in mind. If by these procedures we may save a life, is the life going to be worth saving? I do not think we can always answer that question. Perhaps more exact neurologic data on newborns may provide an answer in the future.

DR. JULIUS H. HESS (CHICAGO).—My interest in this subject concerns particularly the premature infant. In the question of diagnosis, bulging fontanel was mentioned. This is a rather exceptional finding in the premature infant. The skull usually expands so easily that the hemorrhage is generally not so massive as to cause distention. We do not find it often, and so for that reason, it is not ordinarily considered a sign of importance.

The question of asphyxia in the newborn is one sign that has been emphasized, but no one has spoken of cyanosis. To my mind cyanosis is an outstanding diagnostic feature in hemorrhage of the brain in the premature infant. That stands for the full-term infant too. Cyanosis may be constant, and a constant cyanosis in a premature infant usually means a fatal outcome.

As to the question of spinal puncture, I think everything Dr. Montgomery has said about spinal puncture is only too true. I have four lantern slides taken from illustrations found in four standard textbooks—all show marked flexion of the head or neck by the assistant. Not only does this cause great discomfort but it may do harm.

Dr. Dunham quoted Glaser's work in our premature clinic at Michael Reese Hospital. Glaser found that he got his best results with the least trauma by having his child held in an upright sitting position and using a very small needle. The latter is very important. He used, in most instances, a No. 27 needle with a short bevel, one with no sharp point, and that goes in with a boring motion. His conclusions were that microscopic blood in the spinal fluid of newborn infants may be considered as physiologic. As a consequence, intracranial hemorrhage is often diagnosed erroneously. The average amount of spinal fluid one gets from the premature infant is 1 to 2 c.c. I cannot overemphasize the dangers of cisternal puncture. I think every cisternal puncture carries a real risk in cases in which

the cistern is not distended by an abnormal amount of fluid. In tuberculous and epidemic meningitis, it is a fairly safe procedure. To my mind this is one thing one should not turn over to internes to do unless they have had special training or are properly supervised.

On the question of intraventricular puncture I have not much to say because those of you who have dissected a lot of brains in the newborn know that the walls collapse readily under external pressure. I do not think it is hard to get into the lateral ventricles in a case of meningitis when they are distended, but I think it is a great risk in one that has a collapse from external hemorrhage.

About the question of prognosis, Dr. Dunham mentioned the fact that frequently strabismus is the only thing one sees as a remnant of intracranial hemorrhage. When I quote my few statistics, you will find that strabismus is quite outstanding in our group of cases. In those of our premature infants diagnosed as having had intracranial hemorrhage whom we have been able to follow from one to ten years, we found that half of them did not show anything. This is probably due to the fact that there is no great tendency on the part of the clot to organize as shown by Levinson and Saphir. I have seen Levinson's material, and I think it can be explained on the basis of absorption of the clot in the presence of an easily expanding cranium. I am going to give you briefly some figures that will be ready to be published shortly.

During the period from May 1, 1922, to December 31, 1932, a total of 1,427 premature infants were admitted to the premature infant station at Michael Reese Hospital; 986 infants were "graduated" from this institution in that period, and the majority have been under observation throughout their lives. We have a very competent social service organization that looks after the cases that are not returned to their private physicians. Since our material runs a little over 80 per cent charity, we can control it quite well. Since their discharge, there have been 72+ known deaths out of the 986. Of the total 1,427, 440 or 30.8 per cent died. Autopsies were performed on 342, or 77 per cent. Intracranial hemorrhage was found at autopsy in 154, or 45 per cent. In twenty-one cases which did not come to autopsy, the clinical evidence and findings on spinal puncture pointed to the diagnosis of intracranial hemorrhage. Of the 986 who were "graduated," 102 were considered, either while in the station or subsequent to "graduation," as patients with possible intracranial hemorrhages. Whenever we were in doubt, we said this was probably an intracranial hemorrhage. Thirty-three have disappeared or failed to come in for mental or physical examination. Some of these have died since leaving the hospital, but how many we do not know. Sixty-nine have been followed from the time of "graduation" from the station; three of them have died, and the remaining sixty-six have had from one to six physical examinations and mental tests.

Mental studies have been completed by Dr. George Mohr and Dr. Phyllis Bartelme on 250 white children. This group includes our sixty-nine with intracranial hemorrhage.

Analysis of the physical findings of the sixty-six patients with intracranial hemorrhages, who are still living, showed the following: thirty-three have no physical findings which might be referable to intracranial hemorrhage; eleven showed marked physical signs and mental retardation—six of them showing spastic tetraplegia, two spastic diplegia, one hydrocephalus, and one microcephalus with spastic paraplegia —two of these having died since "graduation" from the station; seven infants show moderate physical injury—four of them have moderate spasticity (one of these in both upper and lower extremities and the other three in the lower extremities only), a fifth one has a paresis of the left leg, and two show a hypotonia of the lower extremities; nine other infants show slight injury, such as exaggerated deep

reflexes in six, and three of this group have convergent strabismus. These represent the major physical defects in the 66 cases under observation who have a history of intracranial hemorrhage at birth or who, after discharge from the station, gave evidence of such an injury which had not been diagnosed while they were in the station. It is to be remembered that we have "graduated" 986 infants from this station in the last ten years. There are undoubtedly other cases which have disappeared from observation.

I believe that vigorous attempts at establishing respiration in premature infants are a not infrequent cause in promoting intracranial hemorrhage. I think every obstetrician, when he knows the case is likely to be a premature delivery, should carry the pregnancy as long as he possibly can without endangering the mother too greatly. We find the Drinker apparatus is becoming very popular in obstetrics. I think it does more damage than good in the premature. Occasionally the Drinker is used to good advantage in the full-term infant, but in the premature infant it is almost impossible to synchronize the respirations to the speed of the machine.

DR. JOHN RUHRÄH (BALTIMORE, MD.).—I would like to hear a general expression of opinion as to how much of this hemorrhage is due to the trauma of forceps, or to unduly prolonged labor, and whether cesarean section has lessened it.

DR. HESS.—We have figures in premature births showing that cesarean section has materially lessened the occurrence of intracranial hemorrhage although there have been several cases of hemorrhage. Forceps are rarely used for the premature infant.

DR. DUNHAM.—I think there is no question but that the incidence of birth injury is increased by operative deliveries. In the New Haven study, however, the number of cases of intracranial hemorrhage was too small to relate statistically to the type of delivery.

DR. RUHRÄH.—The reason I am interested is that some years ago we thought a large percentage was due to trauma. Now the pendulum has swung in the other direction. Dr. Dawson of Montgomery, Alabama, told me he thought many of these were due to interference in an effort to hurry labor.

DR. MONTGOMERY.—There have been many studies to show that the percentage of intracranial hemorrhage in breech presentation cases is very high. We are seeing a higher percentage of intracranial hemorrhage in infants delivered in a perfectly normal manner.

DR. DUNHAM.—Any statistics on the relation of the type of delivery to the incidence of intracranial hemorrhage are difficult to interpret because the criteria for the diagnosis of intracranial hemorrhage are usually not known and figures are not available as to the number of operative deliveries performed in which intracranial hemorrhage did not occur.

DR. MONTGOMERY.—The time element in allowing the head to mold is what Crothers feels is important in the prevention of tentorial tears. The explanation he offers of the high incidence in breech deliveries is that the pressure is applied suddenly on the aftercoming head.

DR. W. E. COLLINS (KALAMAZOO, MICH.).—Has anything been said about the use of pituitrin? It is often used in some places.

DR. DUNHAM.—I think the danger to the infant from the use of pituitrin during delivery is well recognized in that the too rapid expulsion of the infant increases the chance of intracranial injury. In the New Haven study there was only one case in 1,000 in which it was used during delivery.

To return for a minute to the discussion of the clinical signs or symptoms of intracranial hemorrhage, I know Dr. Montgomery did not intend to give the impression that there is always a bulging fontanel when intracranial hemorrhage has occurred, but only that when this sign is found it is an important one.

Dr. Hess stressed cyanosis as an important symptom of intracranial injury in the premature infant. His remarks on the progression of the symptoms were also very interesting. I mentioned this in my discussion stating that one sometimes sees no evidence of paralyses early, and yet they may appear as late evidences of intracranial damage.

DR. MONTGOMERY.—The paralyses I have seen at birth have been peripheral rather than central.

DR. DUNHAM.—It is well to bear in mind that a peripheral paralysis apparent soon after birth may clear up rapidly, and one feels optimistic about the infant; but the infant may nevertheless be suffering from some deep-seated cerebral lesion which at the time gives no symptoms.

DR. EDWARD A. WAGNER (CINCINNATI, O.).—In a series of ninety-six premature infants in 1931, we had a mortality rate of 39 per cent. Autopsy showed 14 cases with intracranial hemorrhage. Our series of over 300 cases in three years apparently shows prematurity to be on the increase; the first year there were ninety-six, the second year 104, and this year 126.

Attempts were made to prevent the intracranial hemorrhage that occurs as a spontaneous type, not traumatic. We insist on the giving of blood to all newborn infants under six pounds in weight. In the obstetric department there is an understanding that as soon as these infants are born they are given blood. I do not believe we have had in our series more than one or two cases of spontaneous intracranial hemorrhage. I am not counting the cases that come in with evidence of intracranial hemorrhage. I speak of the late cases that are frequently associated with hemorrhagic disease. Our mortality has dropped from 39 per cent to 25 per cent in the last year. From 75 per cent to 39 per cent the year preceding. Intracranial hemorrhage was the big cause of death. We had 14 cases of intracranial hemorrhage at autopsy. We still insist on the routine giving of blood. We are not drawing any conclusions, but we hope to after we have had 1,000 cases.

DR. F. J. SCHATZ (ST. CLOUD, MINN.).—It is interesting to hear you men discuss the length of time of labor and the use of pituitrin. Time is a great factor in preventing intracranial hemorrhage outside of the premature. Take your full time; let the mother work, and I am willing to wager there will be fewer intracranial hemorrhages. Also forceps delivery, if your patient is permitted to labor, will not cause trouble. You will probably have hemorrhage if you attempt to do a high forceps. Pituitrin will do some damage if given too early. A dead baby is born because of the asphyxiation produced by the tonic contraction of the uterus, which does not allow an easy delivery. If pituitrin is used when there is complete dilatation, it will not cause any trouble unless given in very large doses. If you use 20 to 30 minims, you will have trouble; but 10 to 20 minims will do no harm. In over 3,200 deliveries I have not had more than three full-term children in whom there was a diagnosis of intracranial hemorrhage. I have had some premature infants who were diagnosed as having intracranial hemorrhage.

There is another thing that must be remembered, that we may have all the symptoms and evidence of intracranial hemorrhage, the convulsions, the cyanosis, etc.; a spinal puncture is made, and the fluid is found to be clear and without pressure. In the postmortem you will find the lungs collapsed. You cannot open those lungs. If you will observe those cases, you will sometimes make a diagnosis of another condition and not a diagnosis of intracranial hemorrhage.

Another type of patient that will give tonic convulsions and symptoms of intracranial hemorrhage is the thymus patient. They will develop symptoms within the first twenty-four hours after delivery. They have all the indications of intracranial hemorrhage. X-ray treatment is the procedure of choice. Within twenty-four hours the convulsions will cease, the baby takes its nourishment and goes on normally.

DR DUNHAM.—I think there is no question that Dr. Schatz has stressed a very important factor in saving the infant's life, namely that of conservative conduct of labor.

DR. LOUIS M. EARLE (HOLLYWOOD, CALIF.).—For the past six years in Hollywood, we have been giving blood to the infants in the first twenty-four hours. We have done some coagulation time tests. The prophylactic use of blood given intramuscularly does undoubtedly give benefit.

DR. DUNHAM.—There are two things to remember when one uses a routine method of preventive treatment. First, if one does not know the exact incidence of the condition before the institution of the preventive treatment, one cannot be sure he has prevented it, and second, if a method is used routinely one may not be so careful in picking up abnormal cases. One intramuscular injection of blood will not always cure and may not always prevent hemorrhagic disease in the newborn. The incidence of hemorrhagic disease is not known. In the 939 live births studied in New Haven, three cases of hemorrhagic disease of the newborn occurred, an incidence of 0.3 per cent. These figures cannot be compared with the older figures in which syphilis and other conditions causing hemorrhage were probably not excluded. I do not wish, however, to give the impression that I think the giving of intramuscular blood to the newborn is undesirable.

DR. WAGNER.—We are giving intramuscular blood, and we have seen no cases of spontaneous hemorrhage since giving blood routinely. All babies weighing less than six pounds are given blood. Our statistics bear me out that we have accomplished something. Whether we have an accepted scientific reason for the procedure makes little difference to me if we can show that in our series we are able to diminish the incidence of hemorrhage.

DR. HESS.—After seeing as many intracranial hemorrhages as 40 per cent of all autopsies, we decided that intramuscular blood could do no harm. I do not know that we are accomplishing great good.

DR. MONTGOMERY.—Do you think the way to find out the value of intramuscular blood would be to give it to alternate cases? There are other variabilities which must be taken into consideration, such as type of labor and shape of skull.

DR. WAGNER.—We usually have no difficulty in delivery when the infant is premature.

DR. DUNHAM.—My feeling is that when convulsions develop early in the first twenty-four hours, they are often not of so serious import as when they develop

later. I have seen infants who shortly after birth had slight twitchings or mild convulsions which never occurred again. These infants developed normally, whereas those who developed convulsions at the end of four or five days or later were more prone to show other serious manifestations of damage to the central nervous system.

DR. GEORGE C. KING (FALL RIVER, MASS.).—I had a case similar to that. The baby was apparently normal. There was only a question of whether there was a premature separation of the placenta. The baby had convulsions at the end of twelve hours and more or less edema following intravenous transfusion. The question was whether that had anything to do with it.

DR. HAROLD T. NESBIT (DALLAS, TEXAS).—I have had several instances comparable to this. Each case had been considered that of birth injury by the attending physicians. Where such symptoms as edema, hypertonicity, and positive Chvostek sign are present, I think one is dealing with tetany and cerebral edema rather than a result of trauma or cerebral hemorrhage. In such an instance relief can be promoted by the use of calcium and parathyroid therapy. The picture just described by Dr. King has been reported several times in the literature. I reported six cases in the August, 1932, number of the *American Journal of Diseases of Children*.

Infants presenting this symptom complex are hypertonic. Frequently they are unable to cry aloud, even though grimaces are made. The cry, if present, is usually high pitched in character. Clonic spasms of the extremities occur spontaneously or can be easily provoked by minor disturbances. Often head retraction, irregular respirations, and cyanosis accompany the spasm. Edema of the subcutaneous tissue is frequently encountered, involving more commonly the hands and feet. It is contended by Dr. Ray Shannan of the University of Minnesota that in this type of case edema of the brain as well as the subcutaneous tissue occurs, provoking the definite symptoms of cerebral compression. He believes that the condition is due to a qualitative or quantitative deficiency of calcium.

In attempting to work up a diagnosis of tetany, I found that the total serum calcium was normal—10 mg. per 100 c.c. or higher—in almost every instance. More recently I have made both spinal fluid and serum calcium determinations in this type of case. The spinal fluid calcium proved to be subnormal, whereas the serum calcium was normal in each of four cases. A few hours after administering parathyroid extract the spinal fluid calcium was observed to be elevated to normal, together with an amelioration of the aggravated symptoms. The spinal puncture otherwise did not reveal much; the pressure was increased; no blood was encountered. Since the total serum calcium has proved to be normal in nearly every instance, I consider such a determination of little diagnostic value. I am inclined to believe that the diffusible element is the factor intimately associated with this syndrome. The excellent results accompanying the use of parathyroid very likely are obtained by its action upon the diffusible fraction. It is my custom, however, to use parathyroid and calcium therapy in newborn infants presenting symptoms analogous to those just outlined, since, in addition to the ability to ameliorate tetany and cerebral edema, such therapy decreases the capillary permeability and presumably favorably influences the clotting elements, should the instance be one of cerebral hemorrhage.

Hartzell Ray of the University of California, in studying the diffusible blood calcium in twenty-three newborn infants, observed that symptoms of increased neuromuscular irritability occurred when the diffusible calcium was low. In a personal communication with this author he stated that his interest in diffusible calcium

was stimulated by the findings in these cases of tetany with a total normal calcium and a low diffusible calcium. He treated cases with calcium and parathyroid therapy, and the diffusible calcium came up to approximately normal. Considering the difficulties in the method of determining diffusible calcium in the blood serum, it seems to me that spinal fluid calcium determinations are, for clinical purposes, more accurate and less troublesome. Although some controversy still exists as to whether the spinal fluid calcium is the diffusible fraction, such is in agreement with most observers. The work of Ray and others indicates that a spinal fluid calcium below 5 mg. per 100 c.c. may be accompanied by symptoms of increased neuromuscular irritability.

DR. EARLE.—Do you know whether these hypertonic babies have had any tetany?

DR. NESBIT.—They are all a result of diminished calcium utilization. I find that by giving viosterol and calcium gluconate by mouth they are improved.

DR. EARLE.—I have seen children who have gone all through that cycle without improvement.

DR. NESBIT.—I, too, have had difficulty, but I find that by the utilization of all of the fundamentals of calcium metabolism I know of, good results can be obtained. You frequently have to get the P_H content down by the use of lactose, lactic acid, or ammonium chloride, in addition to viosterol or some form of vitamin D, and sun baths. There are cases which I have not been able to control by oral therapy. If you have difficulty in providing enough calcium by mouth, its subcutaneous use will give a relaxed baby.

DR. KING.—Do you not think that microcephalus might give you a similar condition? It is due to pressure of some sort; either hemorrhage or edema.

DR. DUNHAM.—I would hesitate to make a diagnosis of tetany or to give calcium to an infant when the blood calcium was normal. However, I have had no experience with cases in which spinal fluid calcium determinations have been made.

DR. KING.—This calcium that comes in the spinal fluid is a diffusible calcium—would that not be an indication of calcium in the blood stream?

News and Notes

The Massachusetts Medical Society is conducting this winter a series of lectures for practitioners in various parts of the state. Each secretary of a county society is furnished with a list of the subjects, which includes pediatrics. He then notifies the secretary of the postgraduate course in Boston that he has collected a group of men who wish a lecture weekly, biweekly or monthly, as the case may be, and indicates on the list the subjects selected. A team of two men is then sent from Boston, each one of whom lectures for three-quarters of an hour. Pediatrics has been a popular subject, and pediatric lectures have so far been given in Fitchburg, Brockton, and Greenfield. This method of postgraduate teaching is deservedly popular for it involves no loss of time on the part of the practitioner.

On November 8, the Massachusetts members of the Academy met at dinner to discuss the selection of the Academy members to public health affairs in this state. Twenty-four out of thirty-three members were present. Dr. Richard M. Smith has been in close touch with recent activities of the Children's Bureau in Washington, and Dr. Warren R. Sisson, our state chairman, is on the State Committee for the Child Recovery Program and has been to several meetings of the committee. It is planned to develop forty centers in this state to care for children whose health has been affected by present economic conditions, and it is in just such work that the Academy can be of service. The Massachusetts Department of Public Health and the various welfare agencies concerned in the work are very much interested in having the Academy participate.

The use of Vitamin D yeast milk for infant feeding has increased a great deal in Massachusetts in the last year. The Medical Milk Commissions of Boston, Worcester and Springfield have been very much interested in it and have done all they could to push it. So far, no irradiated milk has been used in this section.

At the Children's Hospital, Dr. Charles F. McKhann is continuing his researches on placental extract as a measles prophylactic and there are indications that it may prove to be of value in other contagious diseases as well.

At a recent meeting of the *New England Pediatric Society*, Dr. James M. Gamble was elected president for the ensuing year.

On December 5, 1933, Dr. Alfred F. Hess of New York died suddenly of heart disease just after making an address to the nurses' graduating class of the Hebrew Home for Infants. At the time of his death he was 58 years of age.

Dr. Hess was graduated from Harvard in 1897 and received his medical degree from the College of Physicians and Surgeons in New York in 1901. His entire medical life was largely spent in scientific studies in the field of pediatrics. His work in the field of rickets was perhaps his outstanding contribution and is known to every pediatrician both at home and abroad. He was a member of many medical and scientific societies, and in 1917 he was awarded the Scott Medal of the Academy of Science of Philadelphia. Dr. Hess was an outstanding figure in pediatrics during the development of what may be called the scientific movement of the past two decades, and his death is a distinct loss to American Pediatrics.

Comments

RECENTLY we listened in on an impromptu discussion among a group of house officers who will soon start in the practice of pediatrics. The question at issue was the formation of a library; what journals, what texts were necessary, what desirable? The advice of some of the older men was being sought and it was interesting to note the difference of opinion. As a matter of fact, no definite conclusion was reached. So much depends on the location where the individual is to start practice. If it is in a city, with a general medical library available, the young practitioner needs relatively little. If the community is such that each practitioner depends upon his own resources, much more is needed. As a general proposition the attitude was reached that a heavy investment in textbooks was unwise. Whether or not a general medical library was available a certain minimum library was deemed essential for every practitioner to have in his office or home. For the pediatricians, the medical school texts in medicine, surgery, and the specialties, as dermatology and ophthalmology, will probably do for a long time. In the specialized field the following additional were, in essential, more or less agreed upon.

1. A modern text on pediatrics for rapid reference.
2. A modern "system" for more detailed study.
3. Three journals: *The Journal of the A. M. A.*
   The Journal of Pediatrics.
   The American Journal of Diseases of Children.

These might be termed the essential minimum. In addition, if not available in a library, the following books should be gradually included.

A text on Infant Feeding.

More journals.

Whether owned or not, the following group of books should be read by every young physician entering on the practice of pediatrics.

Cameron—"The Nervous Child."

Still—"Common Disease of Childhood."

Porter & Carter—"Management of Sick Infant."

The four volumes of the Report of the White House Conference on Growth and Development.

Texts on the mental hygiene of childhood, as,

Richards—"Behavior Aspects of Child Conduct."

Thom—"Normal Youth."

Many more books could, of course, be added to this list. Every one has the feeling that some one text has been of particular value to him as an individual. The important thing is, as Osler said, that the young physician should start a library.

Speaking of books, we have enjoyed reading the recent novel, "Where Is My Mother," by Dr. Charles G. Kerley, although we do not agree with his theme. So far as we know, this is the first time a pediatrician has taken up his pen in the field of fiction. We know this will be of interest to many of our readers.

The Journal of Pediatrics

CONTENTS FOR FEBRUARY, 1934

Original Communications

Encephalographic Studies in Children. Bernard S. Brody, M.D., and Paul F. McAlenney, M.D., New Haven, Conn. ---- 159

The Cause of Death in Infantile Eczema. A. B. Schwartz, M.D., Milwaukee, Wis. ---- 172

A New Pertussis Antigen. J. M. Frawley, M.D., Fresno, M. Stallings, M.D., San Francisco, and V. C. Nichols, A.B., Berkeley, Calif. ---- 179

The Immunization of School Children Against Whooping Cough. J. M. Frawley, M.D., Fresno, Calif. ---- 184

Pertussis. Salmen K. Siebler, M.D., and Samuel Okrent, M.D., Cincinnati, Ohio ---- 188

A Study of Nephrosis in Children. F. Howard Westcott, M.D., and Roger H. Dennett, M.D., New York ---- 191

A Study of the Effect of Preserving Methods on Human Milk. Walter H. Eddy, Ph.D., and Steward G. Morris, M.Sc., New York, N. Y. ---- 208

Recovery From Influenzal Meningitis. D. H. Duncan, M.D., and C. H. Webb, M.D., Shreveport, La. ---- 216

Tetany of the Newborn. John Dorsey Craig, M.D., New York, N. Y. ---- 219

Analysis of Sample Diets and Daily Habits of 206 Children From Data Supplied by Parents. William Palmer Lucas, M.D., Helen Brenton Pryor, M.D., and Saxton T. Pope, Jr., M.D., San Francisco, Calif. ---- 221

The Prophylactic Use and Tolerance of Haliver Oil With Viosterol in Premature and Weakling Infants. Earl W. May, M.D., and Thelma M. Wygant, M.D., Detroit, Mich. ---- 226

A Study of Breast Milk Fat. P. E. Roller, Ph.D., Cleveland, Ohio ---- 238

The Nirvanol Treatment of Chorea. S. W. Marick, M.D., Pittsburgh, Pa. ---- 242

Chronic Sialodochitis. Henry S. Meyer, M.D., Houston, Texas ---- 248

Malaria in the Newborn. J. W. Epstein, M.D., Cleveland, Ohio ---- 251

Pediatric Clinics

Department of Pediatrics, College of Medicine, University of Cincinnati. A. Graeme Mitchell, M.D., Cincinnati, Ohio ---- 256

Critical Review

Nutrition of the Normal Infant. Julian D. Boyd, M.D., Iowa City, Iowa ---- 263

American Academy of Pediatrics

Proceedings Third Annual Meeting of the American Academy of Pediatrics ---- 276

News and Notes

News and Notes ---- 293

Comments

Comments ---- 294

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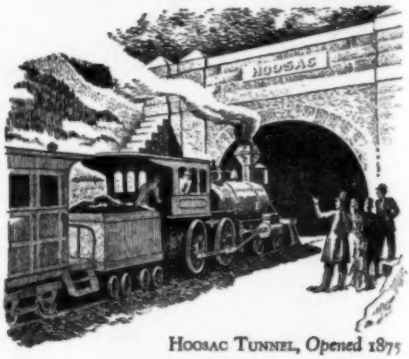

Hoosac Tunnel, *Opened* 1875

Of the important events that transpired in the United States during the year 1875, two are of importance to mankind. The Hoosac Tunnel—drilled under the Green Mountains through 4¾ miles of solid rock—was opened officially to railway traffic. The Maltine Company was also established in the same year and one of the first products it introduced—Maltine With Cod Liver Oil—"Council Accepted"—is still held in high esteem by physicians.

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